IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG, Plaintiffs, v. NOVEN PHARMACEUTICALS, INC., Defendant.	:	Case No. 1:13-cv-00527-RGA Case No. 1:14-cv-00111-RGA

PLAINTIFFS' COUNTER-STATEMENT OF FACTS
AND RESPONSES TO NOVEN'S STATEMENT OF FACTS

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1. Disputed because a POSA could also have been an individual ordinarily skilled in the art. (Tr. 323:3-324:22.)[1]

2. Disputed because a POSA would have had a Ph.D. in chemistry, pharmacy or a related discipline with at least two years' practical experience, or a master's or bachelor's degree in those disciplines and at least four or six years' practical experience, respectively. (Tr. 323:3-13.)

3. Disputed because testing would have been conducted on a case-by-case basis and in response to the specific problems encountered. (SOF 252.)[2]

4. Undisputed.

5. Disputed. Oxidative instability is a chemical, not physical, property; physical properties include melting point, and an example of a physical instability is clumping of a powder. (Tr. 324:23-325:19.) A POSA would not have reasonably expected a compound to oxidatively degrade under pharmaceutically relevant conditions based on its structure. (SOF 253, 351-355, 363, 379, 419, 449.)

6. Disputed that the references in SOF 6 reflect the prior art as a whole. Additional prior art to the '031 Patent includes: PTX162 (EMEA Guidance), PTX184 ('376 Patent), PTX156 (Connors 1979), JTX14 ('961 Patent), JTX16 ('295 Patent), PTX190 ('095 Patent), PTX194 (EP '926), JTX18 (Wilson), PTX215 (1989 USP), PTX216 (1979 USP), JTX26 (Mabey & Mill), PTX174 (Enz 1991), PTX175 (Weinstock 1994), JTX22 (Connors 1986), JTX33 ('548 Patent), PTX185 ('038 Patent), PTX186 ('745 Patent), JTX24 (Boccardi 1994), PTX180 (Magid), and JTX29 (EP '229). (Tr. 341:12-344:14, 346:12-347:13, 348:1-349:23, 367:7-369:3, 370:10-372:20, 381:8-384:14, 385:2-387:24, 406:21-408:10, 420:18-421:18, 424:6-426:16, 439:21-441:3, 443:14-446:15, 483:3-22.) Undisputed that the references in SOF 6 are prior art.

[1] All citations to "Tr." are to D.I. 154-156 in C.A. No. 13-527.

[2] All citations to "SOF" are to the numbered paragraphs of the statement of facts set forth herein.

7. Disputed that the references in SOF 7 represent the prior art as a whole or are material to the validity of the '031 Patent. (Response to SOF 6; Tr. 313:18-314:8.) Undisputed that the references in SOF 7 were not before the Examiner during prosecution of the '031 Patent.

8. Disputed. The statement is not supported by the cited reference, the '031 Patent file history. There is no clear and convincing evidence that the Brij 97 available from Atlas Chemie in West Germany and listed as one exemplary plasticizer in Example 2 of GB '040 (the British counterpart to the '176 Patent) contained an antioxidant. (Tr. 336:21-339:21, 487:16-490:20; JTX19 at 19; JTX9 at 4:9-10 (disclosing Brij 97 from ICI Americas, Inc.); DTX89 (disclosing Brij 97 from Atlas Point).) Noven cites no document connecting ICI Americas, Inc. or Atlas Point to Atlas Chemie of West Germany. (Tr. 270:17-24, 338:6-9.) Even if Brij 97 in GB '040 Example 2 contained an antioxidant, a POSA would have understood that: the antioxidant was present to stabilize the polymer in Brij 97, not rivastigmine; Brij 97 was not required and was only one example among many plasticizers that may be used because Example 2 lists "Plasticizer, e.g. Brij 97"; plasticizers without an antioxidant could be used; and nothing about a plasticizer necessarily implies the presence of an antioxidant in Example 2. (Tr. 268:18-269:5, 338:10-339:21, 340:9-22; JTX19 at 19 (Example 2).) Further, Dr. Kydonieus "didn't testify about how much antioxidant would be in the final formulation of example two of the '040 patent." (Tr. 269:6-11.) Finally, antioxidants were not included in any Brij 97 product from any supplier after January 1, 1991, or as of the '031 Patent invention date, January 12, 1998. (Tr. 277:12-278:10, 295:11-14, 488:1-490:20.)

9. Disputed. (Response to SOF 8.)

10. Disputed that Dr. Klibanov agreed that the listed art is pertinent. (Tr. 511:5-21.) Dr. Schöneich did not base his structural theory on any of the listed art. (Tr. 93:7-10.) The listed

references do not represent the art as a whole. (Response to SOF 6.) Further, the inventors and their development team had extensive experience with rivastigmine and knew its chemical structure but did not expect that it would undergo oxidative degradation or include an antioxidant in any of their early transdermal formulations. (SOF 403-407.)

11. Disputed. The '031 Patent inventors were part of a team of scientists working at Novartis and LTS. (Tr. 428:13-429:17; PTX246 at 66-69.) The team of scientists found in a modern pharmaceutical company would be expected to include organic chemists. (Tr. 97:21-98:15, 122:16-23, 132:20-133:1; Response to SOF 10.)

12. – 23. Undisputed.

24. Disputed. Certain disclosures of GB '040 are limited to transdermal formulations of rivastigmine. (*See, e.g.*, JTX19 at 12-19.)

25. – 30. Undisputed.

31. Disputed. (Response to SOF 8.)

32. Disputed. Dr. Kydonieus admitted that he did not opine on the amount of antioxidant that he believed would have been "contained in the rivastigmine transdermal composition." (Tr. 269:6-11.) At most, Example 2 of GB '040 would have contained nine parts per million ("ppm") antioxidant, and Dr. Kydonieus admitted that he "did not testify whether nine [ppm] is a sufficient amount for a [POSA] to make the compatibility determination with the BHA and citric acid with [the] example two formulation." (Tr. 271:1-15, 272:16-273:2; Response to SOF 8.)

33. Undisputed.

34. Disputed because GB '040 also lacks any stability data or suggestion that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions and it lacks any suggestion to include an antioxidant in any rivastigmine formulation. (SOF 262-269.)

35. Undisputed.

36. Disputed because the experiments in Elmalem were designed to carry out a quantitative comparison of the biological activities of the study drugs, along with positive (physostigmine) and negative (saline) controls. (SOF 289, 312.)

37. Disputed. Elmalem states that "[a]ll drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation." (JTX21 at 1060.)

38. Disputed. Elmalem discloses, among others, aqueous solutions for injection containing only RA_7, antioxidant, and saline. A POSA would have understood that the antioxidant was included in the RA_7 formulations only as a control. There is no evidence that sodium metabisulphite was acting as an antioxidant in the aqueous solutions of RA_7. The prior art as a whole did not teach or reasonably suggest that RA_7 would undergo oxidative degradation under pharmaceutically relevant conditions or require an antioxidant. (SOF 254-260, 308-321.)

39. Disputed. (Response to SOF 38.)

40. Disputed because RA_7 is a racemate, which is a separate compound from its constituent enantiomers. A racemate consists of equal amounts of its two constituent enantiomers. Rivastigmine is one of the constituent enantiomers of RA_7. (Tr. 355:9-18.)

41. Disputed. As of January 12, 1998, it was not known or reasonably suggested in the art that either RA_7 or rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions. (SOF 254-259.)

42. Disputed. Dr. Kydonieus's ratio of rivastigmine to antioxidant is based on his incorrect interpretation of Elmalem. Dr. Klibanov explained that a POSA would not read the "Methods" section of Elmalem to mean that the amount of antioxidant was equal to the weight of drug because "what matters is the absolute concentration of the antioxidant, that is what you want to

keep constant so you don't have to worry about its effect on the observed physiological differences." (Tr. 399:10-400:4.) Because the amounts of drug varied, adding an amount of antioxidant equal to the weight of each drug would require each formulation to contain a different amount of antioxidant. (*Id.*; JTX21 at 1060.) Thus, Dr. Kydonieus's interpretation of Elmalem introduces a new variable, *i.e.*, the amount of antioxidant present in each formulation, and is inconsistent with the otherwise well-controlled design of the Elmalem study. (Tr. 395:16-397:2, 399:10-400:4, 402:20-404:6.)

43. Disputed. Elmalem states that "[e]ach ***drug, RA$_6$***, (1 mg i.v., 2 mg s.c.) ***RA$_7$*** (1 or 2 mg i.v.); ***RA$_{15}$*** (0.25 or 0.5 mg i.v.), ***physostigmine*** (0.05 or 0.1 mg i.v.) or ***saline*** (1 ml), was injected simultaneously with morphine." (JTX21 at 1059 (emphasis added).) A POSA would have understood that Elmalem describes the "drugs" as RA_6, RA_7, RA_{15}, physostigmine and saline, saline being a placebo drug. (SOF 312.) Further, the "Methods" section states that saline included an antioxidant: "All drugs were made up freshly in ***sterile saline, which included*** an equal weight of sodium metabisulphite . . . ." (JTX21 at 1560 (emphasis added).) A POSA would have understood that a stock saline solution was used to prepare the test formulations and that an antioxidant was included in the saline placebo as a control to prevent variability in the test formulations. (SOF 318-319.)

44. Disputed. (Response to SOF 43.)

45. Disputed. A POSA would have understood that because Elmalem was a controlled head-to-head study, variability was minimized so that any observed differences in the test results could be attributed to the drug. (SOF 309-310, 316-317.) Elmalem controlled variability in multiple ways, including by adding an antioxidant to all test formulations. (SOF 317-320.)

46. Disputed. Elmalem does not report any stability test data for RA_7 (Tr. 256:15-19), and

absent data, a POSA would not have made a compatibility determination. (Tr. 486:10-15.)

47. Undisputed.

48. Disputed. The formulations in Elmalem are all aqueous solutions for injection. (JTX21 at 1060; Tr. 257:14-19, 373:2-374:18.) Dr. Kydonieus testified that transdermal formulations do not include aqueous (water-based) solutions and that "you cannot extrapolate directly from one formulation to the other." (Tr. 186:11-24, 258:1-7.) Dr. Kydonieus admitted that "if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch." (Tr. 258:8-13.) A POSA would have known that oxidative degradation is formulation specific and would not have considered Elmalem relevant to transdermal formulations. (Tr. 258:1-13, 418:9-419:19; SOF 338-343.)

49. Undisputed. However, the date of publication of Weinstock 1981 is ten years prior to Elmalem and a POSA would have evaluated each study on its own. (Tr. 409:17-410:9.)

50. Disputed because Erez and Roll are co-authors on Weinstock 1981 whereas Elmalem and Chorev are the co-authors of Elmalem. (JTX30 at 504; JTX21 at 1059.)

51. Disputed. Neither the cited testimony nor Weinstock 1981 supports the statement. Dr. Kydonieus did not opine that the Weinstock 1981 experiments were conducted to "measure" the antagonistic effects of the drugs. (Tr. 153:9-15.) Rather, Weinstock 1981 was a qualitative study to test whether the respiratory depression caused by morphine was due to an effect on the central or peripheral nervous system. (Tr. 410:19-416:19.)

52. – 53. Undisputed.

54. Disputed. Weinstock 1981 would not have changed the way a POSA read Elmalem. (SOF 326-332.)

55. Disputed because the European counterpart to the '807 Patent, EP 0,193,926 ("EP '926"),

which claims priority to the same Israeli priority application as the '807 Patent, published in 1986. (JTX17 at [30]; PTX194 at [30], [43]; Tr. 369:16-371:5.)

56. Undisputed.

57. Disputed because the same Marta Weinstock is also the lead author on Weinstock 1994, joined by Chorev and Enz as co-authors. (PTX175 at 219.)

58. Disputed because the '807 Patent defines the "compounds of the invention" as the millions of compounds fitting the general formula I and their pharmacologically acceptable salts. (JTX17 at 4:21-53; Tr. 353:15-355:2.)

59. Disputed. The '807 Patent, including the cited text, does not disclose a "composition" or "pharmaceutical composition" containing RA_7 as recited in the asserted claims of the '031 Patent because the '807 Patent does not combine RA_7 with an antioxidant. (SOF 282.)

60. Disputed. The statement is not supported by the cited testimony or the '807 Patent. The disclosure of preferred antioxidants in the '807 Patent applies to the "compounds of the invention" generally; it is not specific to any of the more than 8 million compounds of the '807 Patent; and it applies only to sterile compositions for injection and even then only "as required." (SOF 275-279, 334.)

61. Undisputed.

62. Disputed. The disclosure of antioxidants in the '807 Patent is specific to "[s]terile compositions for injection." (SOF 334.) Dr. Kydonieus admitted that "if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch." (Tr. 258:1-13.) A POSA would have known that oxidative degradation is formulation specific and would not consider the '807 Patent relevant to transdermal formulations. (Response to SOF 48; SOF 333-334, 338-345; Tr. 186:6-10, 355:19-356:15,

357:5-358:14.) Further, despite being aware of the teachings of the '807 Patent, the inventor of GB '040 did not teach or reasonably suggest that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions or add an antioxidant to any rivastigmine pharmaceutical formulation. (Tr. 238:12-15, 369:16-372:14; JTX19 at 2.)

63. Undisputed.

64. Disputed. Nicotine is the only drug mentioned in the cited passages. Ebert discloses an unconventional method for manufacturing transdermal devices for "volatile or heat-sensitive drugs, enhancers, or other components that cannot be subjected to drying or heating, such as would occur in an oven." (JTX28 at 5:16-21; SOF 463-474.) There is no evidence that rivastigmine is heat sensitive or volatile or suffers from any of the problems in Ebert associated with the manufacture of nicotine transdermal devices. Rather, GB '040 discloses that rivastigmine formulations can be manufactured using conventional techniques, which would include heating or drying in an oven. (SOF 466, 475.)

65. Disputed. While Ebert contains the quoted statement, the first stated object of Ebert "is to provide a method of fabricating laminated TDD devices that is compatible with volatile or heat-sensitive drugs, enhancers, or other components that cannot be subjected to drying or heating, such as would occur in an oven." (JTX28 at 5:16-21; Response to SOF 64.)

66. Disputed. While Ebert contains the quoted statement, the next sentence provides: "It is to be emphasized that the present invention is particularly adapted to the formulation of drugs . . . that are volatile or heat sensitive and that cannot be readily formulated under conditions where elevated temperatures are required." (JTX28 at 13:35-14:4; Responses to SOF 64, 65.)

67. Disputed. While Ebert contains the quoted statement, nicotine was only known to oxidatively degrade under some pharmaceutically relevant conditions. (Tr. 452:1-5.)

68. Disputed. Neither the cited testimony nor Ebert supports that the antioxidant reduces oxidative degradation of nicotine in "the nicotine transdermal composition." Rather, Ebert states that "***[d]uring fabrication*** of nicotine patches, oxidation is controlled by addition of an antioxidant to the active gel." (JTX28 at 19:23-25 (emphasis added).)

69. Undisputed.

70. Disputed. Ebert states: "To avoid oxidation during storage nicotine should be kept in a dark container and preferably in a dark cabinet. Flooding the storage container with an inert gas, such as nitrogen, also reduces oxidation. During fabrication of nicotine patches, oxidation is controlled by addition of an antioxidant to the active gel." (JTX28 at 19:19-25.) Absent a need to employ Ebert's unconventional manufacturing technique, Ebert would not have motivated a POSA to add an antioxidant. (Tr. 479:8-12; SOF 467-477.)

71. Disputed because Sasaki is an unexamined patent application. (DTX12 at 1.)

72. Undisputed.

73. Disputed because rivastigmine contains numerous functional groups other than an amine, and a POSA would have understood that stability is determined by the molecule as a whole. (SOF 447-449.)

74. Disputed. A POSA would not have understood the teaching of Sasaki to apply to all amine compounds in all transdermal compositions. (SOF 446-457.) As of 1998, there were many thousands of amines, but Sasaki provides data concerning only two amines in one transdermal formulation. (SOF 446-456.) Numerous amine-containing transdermal formulations were not reported to contain antioxidants. (SOF 448-449.) Further, despite the fact that rivastigmine is an amine, Dr. Kydonieus admitted that he would not know whether it would undergo oxidation in an acrylic adhesive. (Tr. 283:14-284:17; *see also* Tr. 282:11-17.)

75. Disputed. (Response to SOF 74.)

76. Disputed. (Response to SOF 74.)

77. Disputed. A POSA would not add an antioxidant to a pharmaceutical formulation unless required. (SOF 421-429.)

78. Disputed. (Response to SOF 74.)

79. Disputed. (Response to SOF 74.)

80. Disputed. Sasaki contains no data demonstrating that either chlorpheniramine or lidocaine undergo oxidative degradation when combined with an acrylic adhesive. (DTX12; Tr. 280:20-281:6, 464:17-465:5.)

81. Disputed. (Response to SOF 74.)

82. Undisputed.

83. Disputed because the Handbook lists pharmaceutical excipients and their properties to the extent they have previously been used in pharmaceutical products. (Tr. 180:13-181:2, 484:21-485:7.)

84. Disputed. A POSA would not have added any excipient, including an antioxidant, unless required. (SOF 421-429.)

85. Disputed. Dr. Kydonieus did not testify that antioxidants are "commonly" used. (Tr. 212:24-213:3.) Further, no FDA-approved transdermal device as of the '031 Patent invention date invention was reported to contain an antioxidant. (PTX157 at 486, 640, 680, 842, 878, 880, 884, 890, 1336, 1365, 1439, 1553, 1568, 2541, 2634.) And a POSA would not have added any excipient, including an antioxidant, unless required. (SOF 421-429.)

86. Disputed. The transcript citation does not support that antioxidants were "commonly employed" in pharmaceutical products. (*See also* Response to SOF 85.)

87. Disputed. The Handbook does not provide "typical" amounts but instead reports that ascorbic acid had been used in the indicated range in aqueous formulations. (JTX8 at 15.)

88. Disputed. The Handbook does not provide "typical" amounts but instead reports that BHT had been used in the indicated ranges. (JTX8 at 47.)

89. Disputed. The transcript citation does not support that a reference to topical formulations applies to transdermal formulations in all contexts.

90. Disputed. The Handbook does not provide "typical" amounts but instead reports that α-tocopherol had been used in the indicated ranges. The Handbook also states that this range had been used for oil or fat based pharmaceuticals, not "pharmaceutical formulations" in general. (JTX8 at 12.)

91. Disputed. The Handbook does not provide "typical" amounts but instead reports that BHA had been used in the indicated ranges. (JTX8 at 45.)

92. Disputed. The Handbook does not provide "typical" amounts but instead reports that propyl gallate had been used in the indicated ranges. The Handbook also states that this range has been used for oil or fat based pharmaceuticals, not "pharmaceutical formulations" in general. (JTX8 at 402.)

93. Undisputed.

94. Disputed. The Handbook provides information on known incompatibilities based on approved products available when the Handbook was published. (Tr. 180:13-181:2, 484:21-485:7.) There is no evidence that any information on the compatibility of rivastigmine with any antioxidant was known when the Handbook was published in 1994 because Novartis had not filed an NDA seeking approval for rivastigmine until 1997, *i.e.*, three years after the Handbook was published. (JTX25 at 1208.)

95. Disputed. While the Handbook contains the quoted language, a POSA would not add an antioxidant unless required. (SOF 421-429.)

96. Disputed. While the Handbook indicates that the antioxidants listed in claim 16 are GRAS, a POSA would not add an antioxidant unless required. (SOF 421-429.)

97. Disputed. The transcript citation does not support that a reference to topical formulations applies to transdermal formulations in all contexts. Further, a POSA would not add an antioxidant unless required. (SOF 421-429.)

98. Disputed. While the Handbook states that tocopherol is vitamin E and ascorbic acid is vitamin C, a POSA would not add an antioxidant unless required. (SOF 421-429.)

99. Disputed. Dr. Kydonieus did not testify regarding incompatibilities with rivastigmine specifically, which has other functional groups aside from an amine. (SOF 395; Response to SOF 94.)

100. Disputed. The Handbook refers to citric acid as an "antioxidant synergist," not an antioxidant. (JTX8 at 123.)

101. – 102. Undisputed.

103. Disputed that the relative bond dissociation energies would inform a POSA whether oxidation would occur, or if it occurs, in what amounts or at what rate. (Tr. 79:16-22, 94:21-95:6, 95:24-96:18; SOF 351-355.) Rather, a POSA would have understood that testing is required to determine whether a drug undergoes oxidative degradation under pharmaceutically relevant conditions because relative bond strengths do not indicate a drug's absolute stability. (SOF 253; Tr. 59:18-23, 437:10-441:18, 443:14-448:14.)

104. Undisputed.

105. Disputed. While Ansel discloses antioxidants, Ansel contains no teaching specific to

rivastigmine. A POSA would not add an antioxidant unless required. (SOF 421-429.)

106. Disputed. While Ansel contains the quoted statements, it contains no teaching specific to rivastigmine. A POSA would not have reasonably predicted whether or to what extent a drug would undergo oxidative degradation under pharmaceutically relevant conditions based on chemical structure; rather, testing would have been required. (SOF 253, 361-363, 379, 418.) Ansel highlights the importance of obtaining "[s]cientific data pertaining to the stability of a formulation" and states that "[o]bviously the *rate* or speed at which drug degradation occurs in a formulation is of prime importance." (DTX91 at 94-95.)

107. Disputed. The transcript citation does not refer to Ansel and says nothing about volatility. Further, Ansel does not say that liquid drugs are "generally volatile." (DTX91 at 87-88.) Neither of Noven's experts presented evidence that rivastigmine was "volatile." GB '040 discloses that rivastigmine formulations can be manufactured using conventional techniques, which would include heating or drying in an oven. (SOF 475.)

108. Disputed. Dr. Kydonieus stated only that "liquids are really more volatile than solid." Dr. Kydonieus admitted that he did not cite any literature showing that rivastigmine is heat sensitive or volatile. (Tr. 289:14-17; Response to SOF 107.)

109. Undisputed.

110. Disputed because the quoted statement is the opening sentence to the chapter concerning stability, not the textbook. (PTX153 at 179.)

111. Disputed. While Modern Pharmaceutics contains the quoted statements, it states only that functional group chemistry can be used to identify "potential" modes of degradation and no functional group present in rivastigmine is listed as potentially oxidatively unstable. (Tr. 421:20-423:22, 528:21-529:8.) Modern Pharmaceutics further states that stability data for the individual

drug in question must be obtained: "It is not the intent of this chapter to document stability data of various individual drugs. Readers are referred to the compilations of stability data [] and to literature on specific drugs [] for this kind of information." (PTX153 at 180.) But no stability data for rivastigmine existed in the prior art. (SOF 359, 362.)

112. Undisputed.

113. Disputed. Linnell hypothesizes that the degradation of nicotine follows a free-radical mechanism and states that "[f]urther work is underway to isolate the proposed hydroperoxide [intermediate] and provide more details on the mechanism of the reaction." (JTX32 at 91; Tr. 106:14-108:4.) Dr. Schöneich did not cite any such further work. (Tr. 106:3-107:8.)

114. Disputed. Dr. Schöneich did not testify that Linnell reports that the oxidation occurred at allylic or benzylic (pyridine ring) carbons. (Tr. 86:19-87:13.) Instead, Linnell states that there is evidence of a free-radical mechanism of oxidation and that "[t]his indicates that nicotine oxidation follows the general mechanism of olefin oxidation . . . ." (JTX32 at 90-91.) Linnell does not explain the "general mechanism" of olefin oxidation. Linnell also states that "[f]urther work is underway to isolate the proposed hydroperoxide [intermediate] and provide more details on the mechanism of the reaction." (JTX32 at 91; Tr. 106:14-108:4.)

115. Undisputed.

116. Undisputed for the disclosures relied on by Noven in this litigation.

117. – 118. Undisputed.

119. Disputed. Remington's states that oxygen can be removed: "In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation." (JTX5 at 1507.)

120. Disputed. While Remington's contains the quoted statements, a POSA would know that there were many potential causes of degradation, not all drugs undergo all types of degradation in pharmaceutical formulations, and a POSA would not add an antioxidant unless required. (SOF 412-429.)

121. Disputed. While Remington's discloses antioxidants, a POSA would not add an antioxidant unless required. (SOF 421-429.)

122. Undisputed.

123. Disputed. The '480 Patent discloses Brij 97 from ICI Americas, Inc.; there is no evidence that Brij 97 available from Atlas Chemie and listed as one exemplary plasticizer in GB '040 Example 2 contained any antioxidant, and no Brij 97 product contained an antioxidant after January 1, 1991. (Response to SOF 8.)

124. Undisputed.

125. Disputed. While ampicillin was formulated as a dry powder and a capsule, oxidative degradation can occur in dry or solid dosage forms, but ampicillin was not reported to undergo oxidative degradation in any formulation. (Tr. 437:10-439:20; SOF 381.)

126. Disputed. While ampicillin has a primary amine, it contains both an amine and a benzylic C-H bond, like dextromethorphan, on which Dr. Schöneich originally relied to advance his structural theory. (Tr. 103:3-11, 443:448:14.)

127. Disputed. While hydroxyzine was formulated as hydrochloride and pamoate salts, oxidative degradation can occur with salt forms, but hydroxyzine was not reported to undergo oxidative degradation in any formulation. (SOF 380.) Further, hydroxyzine hydrochloride is formulated as a syrup and hydroxyzine pamoate is formulated as an oral suspension containing water. (PTX157 at 1992, 2015, 2042.)

128. Disputed. While meclizine was formulated as a hydrochloride salt and a tablet, oxidative degradation can occur with salts or in dry or solid dosage forms but meclizine was not reported to undergo oxidative degradation in any formulation. (SOF 380-381.)

129. Disputed. While mirtazapine was formulated as a tablet, oxidative degradation can occur in dry or solid dosage forms, but mirtazapine was not reported to undergo oxidative degradation in any formulation. (SOF 381.) Further, mirtazapine is formulated as a free base. (PTX157 at 1878; Tr. 558:1-559:2.)

130. Disputed. While benzquinamide was formulated as a hydrochloride salt in a powder, oxidative degradation can occur with salts or in dry or solid dosage forms, but benzquinamide was not reported to undergo oxidative degradation in any formulation. (SOF 380-381.)

131. Disputed. Oxidative degradation was known to occur in dry or solid dosage forms. (Tr. 439:13-20.)

132. Disputed. Oxidative degradation was known to occur with salts. (Tr. 461:21-462:11.)

133. Disputed. A POSA would not have reasonably expected a drug to undergo oxidative degradation in a pharmaceutical composition based on its chemical structure; rather, testing would have been required. (SOF 351-355, 363.) A POSA would also have known that the stability of a drug is influenced by its structure as a whole. (SOF 366, 379, 449.)

134. Disputed. Both Drs. Schöneich and Kydonieus admitted that they did not produce prior art reflecting this practice. (Tr. 99:20-100:10, 236:14-237:4.) A POSA would have understood that "susceptibility" to oxidative degradation does not mean that oxidation will occur in a given formulation because oxidation is formulation specific. (Tr. 95:24-96:9; 232:6-13; 258:8-13; 283:14-284:19; SOF 351-355.) Despite nicotine's known "susceptibility" to oxidative degradation, none of the nicotine transdermal devices commercially available as of 1998 were

reported to contain an antioxidant. (Tr. 108:5-19, 109:6-12, 452:15-454:9; PTX157 at 884, 1439, 1568.) And Dr. Kydonieus did not add an antioxidant to his selegiline test formulations, despite the fact that selegiline has a benzylic C-H bond and a tertiary amine. (Tr. 293:16-24, 294:5-11, 469:12-21; Response to SOF 133.)

135. Disputed. While Ansel contains the quoted statement, it contains no teaching specific to rivastigmine, and many drugs were not reported to undergo oxidative degradation under pharmaceutically relevant conditions. (SOF 370, 375, 413-414, 449.)

136. Undisputed.

137. Disputed. Dr. Schöneich testified that whether a drug with a benzylic C-H bond adjacent to an amine "actually degrades and at which rate, . . . depends on how the formulation is made up." (Tr. 94:21-95:6; Responses to SOF 133, 137.)

138. Disputed to the extent that Noven asserts that oxidative degradation of rivastigmine is catalyzed by heavy metals; there is no evidence of such catalysis.

139. Disputed. Dr. Schöneich testified that "after that reaction happens, this radical here ***will be able to*** react with other components in the formulation" not that it "will" react with other components in the formulation. (Tr. 69:15-17 (emphasis added).)

140. Disputed because a POSA would have understood that whether and to what extent oxidation occurs is formulation specific. (SOF 351-355, 363; Response to SOF 133.)

141. Disputed. A POSA would have understood that whether and to what extent oxidation occurs is formulation specific. (Response to SOF 140.) Further, a POSA would have known that "[k]inetically, [] there is a sufficient energy barrier to many [oxidation] reactions . . . that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation." (Tr. 319:23-321:4, 454:10-455:22; JTX22 at 82.)

142. Disputed. Dr. Schöneich never testified that a POSA would have understood susceptibility to oxidative degradation based on chemical structure to be reasonably "predictable." (*See also* Responses to SOF 103, 133.)

143. Disputed to the extent relative bond dissociation energies would not inform a POSA of whether oxidation occurs in a pharmaceutical formulation, or if it occurs, in what amounts or at what rate. (Tr. 79:16-22, 94:21-95:6, 95:24-96:9, 454:10-455:22.) A POSA would have understood that relative bond strengths do not indicate a compound's absolute stability. (Responses to SOF 103, 133.)

144. Disputed to the extent relative bond strengths would not inform a POSA of whether oxidation occurs in a pharmaceutical formulation, or if it occurs, in what amounts or at what rate. (Tr. 79:16-22, 94:21-95:6, 95:24-96:9; Responses to SOF 103, 133.)

145. Disputed. The statement is not supported by the cited transcript. Dr. Schöneich testified "***if*** you do make a radical as I have said before, this radical can then undergo further reactions . . . ." (Tr. 68:6-8 (emphasis added); *see also* Responses to SOF 103, 133.)

146. Disputed to the extent relative bond strengths would not inform a POSA of whether oxidation occurs in a pharmaceutical formulation, or if it occurs, in what amounts or at what rate. (Tr. 79:16-22, 94:21-95:6, 95:24-96:9; Responses to SOF 103, 133.)

147. Disputed to the extent stabilization of a radical would not inform a POSA of whether oxidation occurs in a pharmaceutical formulation, or if it occurs, in what amounts or at what rate. (Tr. 68:6-8, 76:11-20, 79:16-22, 94:21-95:6, 95:24-96:9; Responses to SOF 103, 133.)

148. Disputed. (Responses to SOF 103, 133.)

149. Disputed. (Responses to SOF 103, 133.) In addition, there is no evidence explaining how these numbers relate to absolute stability. The cited table from Carey & Sundberg reports

bonds with dissociation energies as low as 30 kcal/mol but does not state at what point oxidative degradation will occur under pharmaceutically relevant conditions. (DTX32 at NOV_207996.)

150. Disputed. (Responses to SOF 103, 133.)

151. Disputed that oxidation reactions are only complex once a radical is formed on the drug molecule. A POSA would have understood that the entire oxidation process is complex, including the initiation step. (PTX153 at 183; SOF 356-358.)

152. Disputed. Dr. Schöneich never testified that the initial step is "simple and well-understood." Rather, a POSA would have understood oxidation reactions, including the initiation step "are usually complex, involving multiple pathways for the ***initiation***, propagation, branching, and termination steps." (PTX153 at 183 (emphasis added); SOF 357-358.)

153. Disputed. A POSA would not have reasonably expected a drug to oxidatively degrade under pharmaceutically relevant conditions based on its structure. (SOF 363.) Further, Dr. Schöneich testified that whether a drug will undergo oxidative degradation depends on the chemical environment in which it is placed. (Tr. 79:16-22, 95:4-6, 95:24-96:6.)

154. Disputed. Dr. Schöneich's testimony was not qualified by the mere presence or absence of initiators to oxidation. (Tr. 95:4-6, 95:24-96:6.) Rather, he stated that "if you have a drug which is susceptible to degradation, the extent to which it actually happens, that depends on the environment." (Tr. 95:24-96:6.) Further, there is no evidence that oxidative degradation of rivastigmine is catalyzed by heavy metals.

155. Disputed. (Response to SOF 154.) Further, a POSA would not have reasonably predicted without testing whether the alternatives to antioxidants would work. (Tr. 349:5-13.)

156. Disputed. Physostigmine was not reported to undergo oxidative degradation in any pharmaceutical composition. (SOF 260.) A POSA would have reasonably expected

rivastigmine to be more stable than physostigmine to hydrolysis and at least as stable as physostigmine to oxidation. (SOF 259, 304, 345.)

157. Disputed. A POSA would not have reasonably expected rivastigmine to undergo oxidative degradation in a pharmaceutical composition based on its chemical structure. (SOF 363.) Further, a POSA would not address an unknown stability problem and would not add an antioxidant unless required. (Response to SOF 134; SOF 416, 421-429.) Ansel highlights the importance of obtaining "[s]cientific data pertaining to the stability of a formulation" and states that "[o]bviously the *rate* or speed at which drug degradation occurs in a formulation is of prime importance." (DTX91 at 94-95.) With respect to antioxidants, Ansel notes that "[t]he proper use of antioxidants involves their specific application only after appropriate studies." (DTX91 at 92.)

158. Disputed. While rivastigmine has these three structural features, a POSA would not have reasonably expected rivastigmine to undergo oxidative degradation under pharmaceutically relevant conditions based on its chemical structure. (SOF 363.) A POSA would have understood that the structure of the molecule as whole as well as the environment in which the molecule is placed influence stability. (SOF 343, 366-369; Response to SOF 103.)

159. Disputed. (Responses to SOF 103, 158.)

160. Disputed. (Responses to SOF 103, 158.)

161. Disputed. (Responses to Noven SOF 103, 158.) Further, a POSA would not have considered rivastigmine and nicotine to be structurally similar. (SOF 392-396.)

162. Disputed. Dr. Schöneich cited only one paper on the oxidation of nicotine, Linnell, which he admitted expressly stated that further work was required to understand the mechanism by which nicotine oxidatively degrades. (Tr. 106:14-108:4.) Dr. Schöneich further admitted that

he never studied the oxidation of nicotine. (Tr. 107:9-12; Responses to SOF 113-114.)

163. Disputed. Stability depends on the structure of the molecule as a whole. (SOF 366-369, 379-380, 395-396.)

164. Disputed. While Habitrol may have used airtight packaging, there is no evidence that oxygen or other potential oxidants were removed before packaging. (Tr. 563:4-11.) As of 1998, there were also two other commercial nicotine transdermal formulations (Nicotrol and Prostep) without reported antioxidants or other measures to reduce oxidative degradation. (SOF 401.)

165. Disputed. (Responses to SOF 161-162.)

166. Disputed. It was not known or reasonably suggested in the prior art that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions. (SOF 254-259.) There is no evidence that oxidative degradation of rivastigmine is catalyzed by heavy metals. Oxidative degradation can occur with salts or in dry or solid dosage forms. (SOF 380-381.) Further, a POSA would not have known whether any of the listed methods would work to reduce oxidative degradation without testing. (SOF 432.)

167. Disputed. Neither of Noven's experts testified that the salt form of a drug is "generally less susceptible" to oxidation than the free base form. To the contrary, oxidative degradation was known to occur with salts. (Tr. 461:21-462:11.)

168. Disputed. While other steps to reduce oxidation may have been taken, a POSA would not have known whether the listed methods would work to reduce oxidative degradation without testing. (SOF 380-381, 432; Response to SOF 167.)

169. Disputed. While this occurred with Watson's product, absent a reported antioxidant, a POSA would not presume that an antioxidant was present. (Tr. 559:3-560:4.)

170. Disputed. While the chart indicates the dosage form, there is no evidence that any of the

listed compounds undergo oxidative degradation in any formulation. (Responses to SOF 125-130; Tr. 437:10-439:3.)

171. Disputed. A POSA would not have reasonably expected rivastigmine to undergo oxidative degradation in a pharmaceutical composition based on its chemical structure. (SOF 363.) Further, the listed compounds each have a benzylic C-H bond and include dextromethorphan, on which Dr. Schöneich initially relied to advance his structural theory. (Tr. 103:3-11, 439:21-448:14.)

172. Undisputed that a POSA would have selected Example 2 of GB '040 as a starting point.

173. Undisputed.

174. Undisputed that a POSA would have selected Example 2 of GB '040 as a starting point.

175. Disputed because there is no evidence that the cited knowledge of the inventors was reflective of the knowledge of a POSA. To the contrary, GB '040 states that both the free base and acid addition salts forms of the compounds disclosed therein "exhibit unexpectedly good skin penetration when administered percutaneously." (JTX19 at 13.)

176. Disputed. The transcript citation states only that the side effects associated with bolus injection delivery can be avoided.

177. Undisputed that a POSA would have selected Example 2 of GB '040 as a starting point.

178. Undisputed that there were FDA-approved transdermal formulations as of the invention date of the '031 Patent.

179. Disputed because product stability was known to be important for all pharmaceutical formulations and dosage forms and was not unique to transdermal formulations. (DTX91 at 83; Tr. 328:23-329:14.)

180. Disputed because stability testing is performed on all pharmaceuticals. The specific

testing conducted is determined by problems encountered during development, and the outcome of such testing would not be reasonably predicted in advance. (SOF 252, 419.)

181. Disputed. (Response to SOF 180.)

182. Disputed. A POSA would not have been motivated to combine an antioxidant with rivastigmine in any formulation because the oxidative degradation of rivastigmine was not known or reasonably suggested in the prior art and a POSA would not have added an antioxidant to a rivastigmine pharmaceutical formulation unless required. (SOF 254-259, 421.)

183. Disputed. Dr. Schöneich's cited testimony did not relate to rivastigmine. (*See also* Response to SOF 182.)

184. Disputed. Dr. Schöneich testified that "the POSA would design a matrix of experiments to rapidly verify whether degradation such as oxidation is an issue," not to determine optimal antioxidant concentration. (Tr. 99:7-9.) A POSA would not have been motivated to combine an antioxidant with rivastigmine or conduct any such tests because the oxidative degradation of rivastigmine was not known or reasonably suggested in the prior art. (SOF 254-259, 421.) Further, "[t]he correct choice [of antioxidant] is usually based on extensive stability testing . . . ." (PTX156 at 97.)

185. Disputed. (Responses to SOF 182-184.)

186. Disputed. A POSA would not have been motivated to combine the prior art because (a) rivastigmine's oxidative degradation was not known or reasonably suggested in the prior art and a POSA would not attempt to solve an unknown problem (SOF 254-259, 416); (b) a POSA would not add an antioxidant to a rivastigmine formulation unless required (SOF 421); and (c) a POSA would have understood that oxidative degradation is formulation specific (SOF 343).

187. Disputed. A POSA would not have been motivated to combine the prior art for the

reasons (a) – (c) set forth in Response to SOF 186 and because (d) a POSA would not believe from Sasaki's disclosure of two amines in one transdermal formulation that all amines undergo oxidative degradation because the molecule as a whole determines stability (SOF 456-457); (e) numerous amine-containing transdermal formulations were not reported to contain antioxidants (SOF 448); (f) Dr. Kydonieus admitted that he would not know whether rivastigmine would undergo oxidation in an acrylic adhesive even though it has an amine (Tr. 283:14-284:17); and (g) GB '040 Example 2 teaches that rivastigmine can be combined with an acrylic adhesive and does not suggest that an antioxidant is required (SOF 458).

188. – 189. Undisputed.

190. Disputed. While GB '040 teaches a rivastigmine transdermal formulation, a POSA would not have been motivated to add an antioxidant to the transdermal formulation of GB '040. (Responses to SOF 186, 187; SOF 254-259, 343, 416, 421.)

191. Disputed. Each component set forth in Example 2 is merely exemplary as indicated by the abbreviation "e.g." meaning "for example." (JTX19 at 19; Tr. 338:20-339:5, 339:14-21.) Thus, Example 2 does not describe a specific pharmaceutical composition.

192. Undisputed.

193. Disputed. GB '040 Example 2 does not disclose the antioxidant limitation or its amount "about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition." (Tr. 168:7-19; Response to SOF 8.)

194. – 195. Undisputed.

196. Disputed. (Response to SOF 8.)

197. Disputed. (Responses to SOF 8, 32.)

198. Undisputed that a POSA would have selected Example 2 of GB '040 as a starting point.

199. Disputed. The statement is not supported by the cited transcript. Further, a POSA would not have been motivated to modify the rivastigmine compositions disclosed in GB '040 for the reasons (a) – (c) set forth in Response to Noven SOF 186 and because (d) rivastigmine was not known to be volatile or heat sensitive or suffer from any problems of nicotine addressed by Ebert (SOF 463-466, 482); (e) Ebert does not suggest adding an antioxidant outside of the unconventional active gel technique or to any drug other than nicotine (SOF 470-471); (f) a POSA would not have considered nicotine and rivastigmine to be structurally similar (SOF 395-396); and (g) Elmalem does not disclose a weight percentage of antioxidant (Tr. 398:20-399:1).

200. Disputed. A POSA would have no motivation to combine GB '040 and the Handbook for the reasons (a) – (c) set forth in Response to Noven SOF 186 and because (d) a POSA would have understood that there were other methods to prevent oxidative degradation without using an antioxidant (SOF 430).

201. Disputed. While the Handbook teaches amounts of antioxidant previously used, a POSA would not have added an antioxidant unless required. (SOF 416; Response to SOF 200.)

202. Disputed. A POSA would not have been motivated to modify the rivastigmine compositions disclosed in GB '040 for the reasons (a) – (f) set forth in Responses to Noven SOF 186 and 199 and because (g) the FDA approved nicotine transdermal devices (Nicotrol, Prostep, and Habitrol) were not reported to include an antioxidant, and thus, a POSA would have no reason to conclude that an antioxidant was required in transdermal formulations of rivastigmine (SOF 401). (*See also* Responses to SOF 64, 158-165.)

203. Disputed. (Responses to SOF 186, 199, 202.)

204. Disputed. A POSA would not have been motivated to modify the rivastigmine compositions disclosed in GB '040 for the reasons (a) – (c) set forth in Response to Noven SOF

186 and because (d) the compositions of Elmalem are aqueous solutions for injection and Dr. Kydonieus acknowledged that transdermal devices do not contain aqueous (water-based) solutions (SOF 335; Tr. 186:11-16.); and (e) Dr. Kydonieus never testified that GB '040 Example 2 is in solution but made the broader statement that in a transdermal device, the drug has to be in solution (Tr. 186:11-16), however, GB '040 states that the transdermal composition can be in solid form (JTX19 at 16). Dr. Kydonieus also admitted that "if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch." (Tr. 258:8-13; *see also* Tr. 283:12-284:17.)

205. Disputed. (Responses to SOF 186, 199, 202, 203.) A POSA would have understood that Elmalem added an antioxidant to RA_7 as a control, not because RA_7 undergoes oxidative degradation. (SOF 317.) There is no stability test data in Elmalem showing that the antioxidant reduced any oxidative degradation. (SOF 307-308.) In addition, GB '040, Enz 1991(which published the same year as Elmalem), and Weinstock 1994 (which published after Elmalem), each formulate rivastigmine with no antioxidant. (SOF 257-258, 264, 325.)

206. Disputed. A POSA would not have been motivated to modify the rivastigmine compositions disclosed in GB '040 for the reasons (a) – (c) set forth in Response to SOF 186 and because (d) the '807 Patent mentions antioxidants only in connection with "sterile compositions for injection" (SOF 334); (e) Dr. Kydonieus never testified that Example 2 of GB '040 is in solution but made the broader statement that in a transdermal device, the drug has to be in solution (Tr. 186:11-16), however, GB '040 states that the transdermal composition can be in solid form (JTX19 at 16); and (f) Dr. Kydonieus admitted that "if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch" (Tr. 258:8-13; *see also* Tr. 283:12-284:17; Response to SOF 62).

207. Disputed. (Response to Noven SOF 206.) Further, the '807 Patent contains no data concerning the stability of any of the millions of compounds of the invention, including RA_7. (SOF 281.) The disclosure of antioxidants in the '807 Patent is not specific to any compound of the invention, let alone RA_7. (SOF 276-277.) The '807 Patent states that the preferred compounds of the invention have greater chemical stability than physostigmine. (SOF 255, 279.) In addition, GB '040 (which cites the European counterpart to the '807 Patent), Enz 1991 and Weinstock 1994 (both of which published after the '807 Patent), each formulated rivastigmine with no antioxidant. (SOF 257-258, 284-287.)

208. Disputed. (Responses to SOF 186, 187.)

209. Disputed. (Responses to SOF 186, 187.)

210. Disputed. The statement is not supported by the transcript citations. Further, although a POSA would strive to develop stable pharmaceutical products, a POSA would not have been motivated to combine Sasaki with GB '040. (Response to SOF 187.) Because GB '040 does not teach or reasonably suggest that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions, a POSA would not have added an antioxidant to address an unknown stability problem. (SOF 421-422.)

211. Disputed. A POSA would not have been motivated to apply the amounts of antioxidant disclosed in Sasaki to GB '040 Example 2 to address an unknown stability problem. (Response to SOF 187.)

212. Disputed. A POSA would not have been motivated to combine the prior art for the reasons (a) – (f) set forth in Responses to SOF 186 and 199. (*See also* Responses to SOF 65, 158-165.)

213. Disputed. A POSA would not have been motivated to combine the prior art for the

reasons (a) – (g) set forth in Responses to SOF 186 and 187.

214. Disputed. A POSA would not have been motivated to combine Elmalem with the Handbook for the reasons (a) – (c) set forth in Response to SOF 186 and because (d) a POSA would have understood that Elmalem added an antioxidant to RA_7 as a control, not because RA_7 undergoes oxidative degradation (SOF 317); and (e) GB '040, Enz 1991 (which published the same year as Elmalem), and Weinstock 1994 (which published after Elmalem), each formulated rivastigmine with no antioxidant (SOF 257-258, 264, 325).

215. – 216. Undisputed.

217. Disputed. A POSA would not have been motivated to combine GB '040 and the Handbook for the reasons (a) – (c) set forth in Responses to SOF 186 and 212 and because (d) a POSA would have understood that there were other methods to prevent oxidative degradation without using an antioxidant (SOF 430).

218. Disputed. Ebert states: "To avoid oxidation during storage nicotine should be kept in a dark container and preferably in a dark cabinet. Flooding the storage container with an inert gas, such as nitrogen, also reduces oxidation. During fabrication of nicotine patches, oxidation is controlled by addition of an antioxidant to the active gel." (JTX28 at 19:19-25.) Dr. Kydonieus did not testify as to what amount of BHT he believed would carry-over to the transdermal patch in Ebert and there is no evidence that the amount, if any, would be effective to reduce oxidation of nicotine in the transdermal patch. (Response to SOF 68; SOF 469-471.)

219. Disputed. A POSA would not have believed from Sasaki's disclosure of two amines in one transdermal formulation that all amines undergo oxidative degradation. (SOF 456-457.) Further, Sasaki does not disclose that tocopherol is compatible with all amines or that the amount disclosed would be effective in other formulations. (Responses to SOF 73-80.)

220. Disputed. A POSA would not have been motivated to combine Elmalem with the Handbook. (Response to SOF 214.)

221. Disputed. Dr. Kydonieus's opinion is based on an improper reading of Elmalem. (Responses to SOF 38, 42.) Further, the ratio of antioxidant to rivastigmine proposed by Dr. Kydonieus (2:1) is much greater (400 fold) than the ratio from the '031 Patent, on which he relies to assert that the amount is "effective to stabilize" (0.005:1). (Tr. 202:7-23, 260:12-16, 262:23-263:5.) Dr. Kydonieus admitted that "[i]t is not always the case that adding a higher concentration of an antioxidant will improve (or keep the same) the stability of the formulation." (Tr. 263:23-264:7.)

222. Disputed. The statement is not supported by the cited testimony or the '031 Patent. The examples set forth in the '031 Patent do not require that oxidation be prevented as some degradation still occurred in the antioxidant-containing samples. (JTX1 at 4:20-30, 7:15-38; Response to SOF 221.)

223. Undisputed.

224. Disputed. A POSA would not have been motivated to modify the claims of the '176 Patent for the reasons set forth in Responses to SOF 186, 187, 199, 204 and 206.

225. – 233. Undisputed.

234. Disputed. A POSA would not have been motivated to modify the claims of the '176 Patent for the reasons set forth in Response to SOF 186, 187, 199, 204 and 206.

235. Undisputed.

236. Disputed. (Responses to SOF 186, 187, 199, 204, 206.)

237. Undisputed.

238. Disputed. A POSA would not have been motivated to modify the claims of the '176

Patent for the reasons set forth in Response to SOF 212.

239. Disputed. (Responses to SOF 8, and 197.) Further, BRIJ 97 is not mentioned in the claims of the '176 Patent.

240. Disputed. (Responses to SOF 212-214.)

PLAINTIFFS' COUNTER-STATEMENT OF FACTS

I. The Discovery Of Rivastigmine's Oxidative Degradation Is A Patentable Invention

241. The invention date for the two asserted claims of the '031 Patent is January 12, 1998. (JTX1 at [30]; Tr. 321:24-322:8.)

242. Claim 7 of the '031 Patent recites transdermal devices comprising the drug rivastigmine and an antioxidant. (JTX1 at 8:14-21, 49-51.)

243. Claim 16 of the '031 Patent recites methods of stabilizing comprising the drug rivastigmine and an antioxidant. (JTX1 at 9:10-10:3.)

244. The '031 Patent inventors discovered the previously unknown problem that the rivastigmine "transdermal composition in [GB '040] . . . degrade[s], possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around [rivastigmine] and its storage in air-tight packaging" and found that an antioxidant could address that problem. (JTX1 at 1:22-39, 4:5-7; Tr. 433:22-435:10.)

245. The '031 Patent inventors discovered the actual oxidative degradation of rivastigmine in pharmaceutical formulations. (JTX1 at 1:22-39, 4:20-13 ("Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60^{o} C."), 7:16-52; Tr. 433:22-435:10.)

246. Prior to the discovery of the oxidative degradation problem, the use of an antioxidant was thought to be unnecessary with rivastigmine. (JTX1 at 4:8-10; Tr. 429:18-433:18.)

247. The U.S. counterpart of GB '040, the '176 Patent, was considered by the Examiner during prosecution of the '031 Patent. (Tr. 333:14-20; JTX3 at 1063.)

248. The '176 Patent contains all the information on which Noven relies from GB '040. (Tr. 333:21-334:2.)

249. The '807 Patent was considered by the Examiner during prosecution of the '031 Patent. (Tr. 353:7-9; JTX3 at 1083.)

250. The Examiner did not question the validity of the '031 Patent over the '176 Patent or the '807 Patent. (Tr. 334:3-23, 353:10-14; JTX3 at 1077 ("As acknowledged by the fact that the Office Action contains no rejection over the prior art, the composition and method related to this aspect of Applicants' invention are both novel and unobvious.").)

II. Person Of Ordinary Skill At The Time Of The Invention

251. A POSA would have understood that drug formulation is complex and unpredictable. (Tr. 323:14-324:22.)

252. When formulating a drug, a POSA would have made rational, data-driven decisions supported by testing and would have carried out testing on a case-by-case basis and in response to specific problems that arose. (Tr. 323:14-324:22.)

253. A POSA would not have reasonably expected a compound to undergo oxidative degradation under pharmaceutically relevant conditions based on its structure; rather, testing would have been required to determine whether such degradation would occur. (Tr. 95:24-97:2, 147:3-148:6, 231:21-232:13, 258:8-13, 283:14-284:17, 293:16-295:3, 296:3-11, 318:8-319:9, 323:14-326:7, 330:24-331:10, 454:10-456:8.)

III. The Art As A Whole Teaches That Rivastigmine Is Stable And Does Not Require An Antioxidant

254. GB '040 discloses rivastigmine, but Dr. Kydonieus admitted that GB '040 "does not expressly disclose an antioxidant" or "suggest adding an antioxidant to any of the rivastigmine formulations disclosed therein." (Tr. 235:12-236:1, 238:12-15; *see also* Tr. 332:1-333:4.)

255. The purpose of the '807 Patent was "to provide new carbamate derivatives which show greater chemical stability than physostigmine," and the '807 Patent teaches that the greater *in vivo* activity of RA_7 compared to physostigmine may be due to "greater chemical stability." (JTX17 at 3:37-39, 11:21-29; Tr. 245:23-246:4, 359:20-360:24.)

256. To the extent Elmalem discusses stability, it states that RA_7 has "a greater chemical stability . . . than that of physostigmine." (JTX21 at 1059; Tr. 406:4-20.)

257. Weinstock 1994, a paper published in 1994 by Drs. Martha Weinstock and Michael Chorev, the same authors of Elmalem and inventors of the '807 Patent, as well as Dr. Albert Enz, states that rivastigmine "showed superior chemical stability . . . physostigmine" and does not add an antioxidant to rivastigmine or reasonably suggest that rivastigmine undergoes oxidative degradation in the formulations tested. (Tr. 406:21-408:21; PTX175 at 219.)

258. Enz 1991, a paper published in 1991 by Dr. Albert Enz, the inventor of GB '040, states that rivastigmine "appears to have greater chemical stability . . . than does physostigmine" and does not add an antioxidant to rivastigmine or reasonably suggest that rivastigmine undergoes oxidative degradation in the formulations tested. (Tr. 406:21-408:21; PTX174 at 272.)

259. A POSA would have understood that RA_7's "greater chemical stability" than physostigmine included oxidative stability. (Tr. 359:20-360:21, 364:18-365:5 (a POSA would not have understood the preferred antioxidants disclosed in the '807 Patent to relate to RA_7 "because . . . these preferred compounds of the '807 patent invention, such as RA_7, have superior

stability, for example, greater stability than physostigmine"), 406:4-408:21 (a POSA would understand from RA_7's "greater chemical stability" that it is "stable in aqueous solution"); PTX153 at 181-85 (oxidative stability encompassed in chemical stability.)

260. As of 1998, physostigmine was known to hydrolyze in aqueous solution, but it was not known to oxidatively degrade in any pharmaceutical formulation. (Tr. 379:16-381:7, 466:8-468:7, 554:5-14; JTX17 at 1:32-34, 2:45-47; JTX33 at 8:50-65; JTX18 at 456.)

A. GB '040 Is Silent On Rivastigmine's Instability Or Requirement For An Antioxidant

261. GB '040 discloses the structure of rivastigmine. (Tr. 45:11-24; JTX19 at 1.)

262. GB '040 does not state that the structure of rivastigmine suggests susceptibility to oxidation. (Tr. 240:4-10.)

263. Dr. Kydonieus admitted that GB '040 does not disclose: any stability data on rivastigmine; "the rate or extent of oxidation of rivastigmine in general or in a formulation"; "any data that would suggest that rivastigmine would undergo oxidative degradation under pharmaceutically relevant conditions"; or the structure of any rivastigmine oxidative degradation products. (Tr. 233:5-11, 234:12-16, 238:16-239:6.)

264. GB '040 discloses rivastigmine in a transdermal formulation but does not teach or reasonably suggest oxidative instability or the use of an antioxidant with rivastigmine. (Tr. 238:12-15, 332:1-333:4; JTX19 at 19 (Example 2).)

265. GB '040 also discloses administering rivastigmine orally and by injection but does not teach that rivastigmine undergoes oxidative degradation, or reasonably suggest the use of an antioxidant with rivastigmine, in any pharmaceutical composition. (Tr. 335:14-24; JTX19 at 3.)

266. None of the examples in GB '040 includes an antioxidant or takes any other precautions to reduce oxidative degradation. (Tr. 336:1-7.)

267. None of the excipients in Example 2 of GB '040 is an antioxidant. (Tr. 336:21-337:5; JTX19 at 19 (Example 2).)

268. There is no teaching in GB '040 that would have led a POSA to reasonably expect that rivastigmine had an oxidative degradation problem or required an antioxidant. (Tr. 336:13-20, 339:22-340:8.)

269. Based on GB '040, a POSA would have reasonably expected that rivastigmine was stable and would not have tried to solve an unknown stability problem. (Tr. 350:1-12.)

270. No prior art after the 1988 publication of GB '040 discloses a rivastigmine transdermal device. (Tr. 350:13-351:10.)

B. The '807 Patent Does Not Teach Or Reasonably Suggest That Rivastigmine Undergoes Oxidative Degradation Or Requires An Antioxidant

271. Because GB '040 does not teach or reasonably suggest any oxidative degradation problem, a POSA would not have been motivated to combine GB '040 with the '807 Patent to solve an unknown degradation problem. (Tr. 351:17-353:6.)

272. The '807 Patent discloses a general formula encompassing over eight million phenyl carbamate compounds that are defined as the "compounds of the invention." (Tr. 353:15-355:2; JTX17 at 1:9-12, 4:21-53.)

273. The '807 Patent also identifies eight preferred "compounds of the invention," one of which is RA_7. (Tr. 355:4-8, 359:20-360:24; JTX17 at 5:40-50.)

274. There is no reasonable suggestion in the '807 Patent that RA_7 undergoes oxidative degradation under pharmaceutically relevant conditions, or requires an antioxidant. (Tr. 351:11-353:6.)

275. The '807 Patent discloses antioxidants among a large list of possible excipients that may be added "as called for by accepted pharmaceutical practice" or "as required," meaning that a

POSA would not add them unless required. (JTX17 at 7:15-53; Tr. 361:2-362:4.)

276. The disclosure of antioxidants relates to the "compounds of the invention" generally; it is not specific to any of the more than 8 million compounds of the '807 Patent. (Tr. 364:11-365:11; JTX17 at 7:15-53.)

277. The disclosure of preferred antioxidants is not specific to the millions of "compounds of the invention" encompassed by "general formula I" of the '807 Patent. (Tr. 353:15-355:2, 364:11-365:11; JTX17 at 4:21-53, 7:51-53.)

278. A POSA would have expected that the eight million-plus "compounds of the invention" to have different stabilities that would only be determined through testing. (Tr. 365:12-24.)

279. A POSA would not have understood the teaching of preferred antioxidants to relate to the preferred compounds of the invention "because . . . these preferred compounds of the '807 patent invention, such as the RA_7, have superior stability." (Tr. 364:18-365:5.)

280. Dr. Kydonieus admitted that the '807 Patent does not "provide any ranges for any of the antioxidants that it says are preferred." (Tr. 254:10-13; *see also* Tr. 366:1-5.)

281. Dr. Kydonieus admitted that the '807 Patent does not disclose any stability data for RA_7 or regarding the rate or extent of oxidative degradation, indicating an antioxidant was required. (Tr. 253:16-19, 254:21-255:2; *see also* Tr. 359:16-19; SOF 253.)

282. Dr. Kydonieus admitted that none of the examples in the '807 Patent combines RA_7 with an antioxidant. (Tr. 255:3-6.)

283. While the '807 Patent contains no stability data, the '807 Patent portrays the stability of RA_7 in a positive light. (Tr. 253:16-19, 254:21-255:2, 255:3-6, 351:11-353:6, 359:20-360:24; JTX17 at 3:37-39, 11:21-29.)

284. GB '040 cites the European counterpart to the '807 Patent, European patent application

193,926 ("EP '926"). (Tr. 369:16-370:9; JTX19 at 2.)

285. EP '926 was published in 1986, before the 1987 priority date of GB '040. (Tr. 370:23-372:1; PTX194 at [43]; JTX19 at [30].)

286. EP '926 contains the '807 Patent disclosures on which Noven relies. (Tr. 370:10-17.)

287. Although the inventor of GB '040, Dr. Albert Enz, was aware of the teachings of the '807 Patent, he did not add an antioxidant to rivastigmine in any formulation, including a transdermal formulation, and did not teach or reasonably suggest that there was an oxidative degradation problem with rivastigmine or that rivastigmine required an antioxidant. (Tr. 332:1-333:4, 335:14-24, 371:6-372:14.)

C. Elmalem Does Not Teach Or Reasonably Suggest That Rivastigmine Undergoes Oxidative Degradation Or Requires An Antioxidant

288. Because GB '040 does not teach or reasonably suggest any oxidative degradation problem, a POSA would not have been motivated to combine GB '040 with Elmalem to solve an unknown degradation problem. (Tr. 332:1-333:4, 335:14-24, 372:22-374:18.)

289. Elmalem discloses a study comparing the ability of then-novel anticholinesterases RA_6, RA_7 and RA_{15} with that of physostigmine and a saline placebo to antagonize the respiratory-depressant effects of morphine in rabbits. (Tr. 376:9-377:3, 395:16-397:2; JTX21 at 1059.)

290. To understand Elmalem, a POSA would have considered what was known in 1991, the time Elmalem was published, about the stability of phenyl carbamates, and the purpose of the Elmalem study. (Tr. 374:20-376:8; JTX21 at 1059.)

1. A POSA Would Have Reasonably Expected Diaklyl Carbamates Like RA_7 To Be More Stable In Aqueous Solution Than Monomethyl Carbamates Like Physostigmine

291. A POSA reading Elmalem would have appreciated the structural difference between physostigmine and RA_7 and would not have reasonably expected RA_7 to oxidatively degrade in aqueous solution. (Tr. 392:4-393:1.)

292. Physostigmine is a monomethyl carbamate, whereas RA_7 is a dialkyl carbamate. (Tr. 377:11-379:15.)

293. It was known that monomethyl carbamates, such as physostigmine, tend to be unstable and hydrolyze readily in aqueous solution. (Tr. 379:16-380:8; JTX17 at 1:32-34, 2:45-47.)

294. The art as of 1991, taught that in aqueous solution, physostigmine must be prepared with an antioxidant to reduce the oxidative degradation of its hydrolytic degradant eseroline. (JTX17 at 1:29-34; JTX18 at 456; Tr. 379:16-383:4.)

295. Eseroline was known to oxidatively degrade forming a colored compound, called rubreserine, and its degradation products. (JTX18 at 456; Tr. 381:8-383:4.)

296. It was known that physostigmine formulations should not be used if more than slightly discolored because discoloration indicates that degradation to rubreserine and its degradation products has occurred, and the effects of those degradants on the pharmaceutical formulation or an experiment were not known. (Tr. 383:7-384:11; JTX215 at 1079; JTX216 at 624.)

297. Dialkyl carbamates such as RA_7 and rivastigmine were known to be much more stable towards hydrolysis than monomethyl carbamates like physostigmine in aqueous formulations. (Tr. 384:16-389:7; JTX18 at 457; JTX26 at 133.)

298. Experiments showed that, for example, converting a monomethyl carbamate to a dialkyl carbamate could increase the half-life more than 50,000 fold from 8.5 days to 1,200 years under otherwise the same conditions. (Tr. 385:2-387:19; JTX26 at 133.)

299. As another example, greater hydrolytic stability compared to the monomethyl carbamate physostigmine was obtained with the dialkyl carbamate neostigmine, which was shown to be stable in aqueous solution even under boiling. (Tr. 388:2-389:7; JTX18 at 457.)

300. Dialkyl carbamates as a class were considered stable to hydrolysis. (Tr. 388:2-389:7.)

301. A POSA would have expected dialkyl carbamates as a class to be stable to hydrolysis based on their structure because there "had been a great deal of experimental studies" conducted over many decades to elucidate the mechanisms of hydrolysis of monomethyl and dialkyl carbamates. (Tr. 389:8-391:14; JTX26 at 133-34.)

302. From these studies, it was known that monomethyl and dialkyl carbamates undergo hydrolysis by different mechanisms: monomethyl carbamates undergo hydrolysis when a hydroxide group (HO-) attacks the hydrogen bonded to the nitrogen of the carbamate group, whereas with dialkyl carbamates that reaction cannot take place because there is no hydrogen attached to the nitrogen of the carbamate group to attack. (Tr. 389:8-391:14; JTX26 at 133-34.)

303. Experimental studies showed that the mechanism of hydrolysis of monomethyl carbamates was more facile and much faster than the mechanism of hydrolysis of dialkyl carbamates. (Tr. 389:8-391:14; JTX26 at 133-34.)

304. Because RA_7 is a dialkyl carbamate, a POSA would have reasonably expected RA_7 to be stable toward hydrolysis in aqueous solution, and thus there would be no subsequent oxidative degradation of hydrolytic degradants as with physostigmine. (Tr. 392:4-393:1.)

305. The other structural differences between physostigmine and RA_7 do not change the fact that RA_7 cannot undergo hydrolysis by the same facile mechanism by which physostigmine degrades. (Tr. 393:2-14.)

306. The art did not teach that RA_7 or rivastigmine suffered from any form of chemical

instability or required an antioxidant in any pharmaceutical formulation. (Tr. 313:1-314:8, 405:5-20.)

2. Elmalem Was A Well-Controlled Study To Compare The Relative Effects Of Three New Agents With Those Of Physostigmine And A Saline Placebo

307. Dr. Kydonieus admitted that: "Elmalem [is] not a stability study" (Tr. 255:22-256:2); "Elmalem does not disclose any data regarding the rate or extent of oxidative degradation of RA_7" (Tr. 256:15-19); and Elmalem does not disclose "how much degradation . . . took place in the Elmalem formulations without an antioxidant" (Tr. 225:21-24).

308. Elmalem discloses no testing to show that rivastigmine oxidatively degrades under pharmaceutically relevant conditions or requires an antioxidant in any pharmaceutical formulation. (Tr. 225:21-24, 255:22-256:2, 256:15-19, 405:21-406:3.)

309. Elmalem reports the findings of a well-controlled experiment, to compare the effects on respiratory depression in rabbits of three new agents, including RA_7, with that of physostigmine and a saline placebo. (JTX21 at 1059; Tr. 395:16-397:2, 395:16-397:2, 402:20-403:21.)

310. A controlled experiment is one in which any variability, other than the variable being studied such as the drugs in Elmalem, that can be eliminated is eliminated. (Tr. 401:20-402:19.)

311. Elmalem states that "[e]ach drug, ***RA_6***, (1 mg i.v., 2 mg s.c.) ***RA_7*** (1 or 2 mg i.v.); ***RA_{15}*** (0.25 or 0.5 mg i.v.), ***physostigmine*** (0.05 or 0.1 mg i.v.) or ***saline*** (1 ml) was injected simultaneously with morphine." (JTX21 at 1059 (emphasis added); Tr. 397:18-398:19.)

312. Elmalem thus describes the "drugs" as RA_6, RA_7, RA_{15}, physostigmine and saline—saline being a placebo. (Tr. 397:18-398:19.)

313. Saline is simply a solution of sodium chloride in water. (Tr. 397:11-15.)

314. Elmalem states that "[a]ll drugs," including the saline placebo, "include an equal weight of sodium metabisulphite," and thus teaches that each "drug" formulation was prepared in the

same way, with an equal weight of antioxidant. (JTX21 at 1060; Tr. 397:4-10, 399:2-9.)

315. Physostigmine was known to be unstable in aqueous solution and require an antioxidant. (JTX17 at 1:29-34; JTX18 at 456; Tr. 379:16-383:4.)

316. If physostigmine were administered with an antioxidant, and the other "drugs" without an antioxidant, there would be no way to determine whether any observed difference in the effect was attributable to the drug or the antioxidant. (Tr. 399:10-400:4, 400:23-401:7, 401:20-402:19, 403:23-404:6.)

317. Because physostigmine required an antioxidant in aqueous solution, Elmalem added an antioxidant to all other "drugs," including the saline placebo, as a control. (Tr. 400:5-401:7, 404:7-405:4.)

318. A POSA would have understood that Elmalem prepared a stock solution of sterile saline with an antioxidant, from which each drug including the placebo was prepared and thus, all "drugs" "included an equal weight of sodium metabisulphite." (Tr. 399:2-9, 400:5-401:7; JTX21 at 1060.)

319. Preparing a stock solution is an easier method and ensures that each formulation is the same except for the drug being studied, and thus any observed differences in the effects can be attributed to the drug. (Tr. 400:23-402:19.)

320. That an antioxidant was added to RA_7 only as a control is further supported by the fact that Elmalem controlled for other variables, including the route of administration (by injection), and minimized the effects of differences between rabbits tested (by testing at least four rabbits per treatment, using rabbits of similar size, calculating dosages per kilogram of body weight, analyzing blood samples before and after treatment, monitoring changes in body temperature, and normalizing respiration rates). (Tr. 402:20-404:6; JTX21 at 1059-60.)

321. That an antioxidant was added to saline alone further confirms that all "drugs" other than physostigmine included an antioxidant as a control, and not to reduce oxidative degradation, because saline does not undergo oxidative degradation. (Tr. 404:7-405:4.)

322. The "Methods" section of Elmalem explicitly states that the sterile saline included the antioxidant sodium metabisulphite: "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite . . . ." (JTX21 at 1060; Tr. 397:4-17.)

323. A POSA would have understood that an "equal weight of sodium metabisulphite" means that "each drug solution had [an] equal weight or the same quantity of sodium metabisulphite, including the saline placebo solution." (Tr. 399:2-9; JTX21 at 1060.)

324. Elmalem would not have told a POSA that oxidation of RA_7 was occurring in aqueous solution. (Tr. 225:21-24, 255:22-256:2, 256:15-19, 405:21-406:3.)

325. That the Elmalem authors did not add an antioxidant to rivastigmine in their subsequent Weinstock 1994 paper demonstrates that they did not believe or reasonably expect rivastigmine to be oxidatively unstable or require an antioxidant. (SOF 257; Tr. 406:21-408:21; PTX175 at 219.)

326. Weinstock 1981 would not have changed the way a POSA would read Elmalem because the two studies were conducted 10 years apart for very different purposes. (Tr. 409:17-410:9; JTX21 at 1060; JTX at 504.)

327. Weinstock 1981 was not a controlled head-to-head study comparing the relative effect of drugs; rather, it studied the "hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous system." (JTX30 at 504; Tr. 410:19-412:13, 416:21-417:5.)

328. To address its stated hypothesis, Weinstock 1981 used drugs such as physostigmine and

neostigmine, which were known at the time to affect either the central or peripheral nervous systems. (Tr. 410:19-415:3; JTX30 at 504, 507.)

329. Weinstock 1981 drew a qualitative conclusion that, because centrally acting physostigmine could overcome the respiratory depressant effect of morphine, morphine's respiratory depressant effect must be caused by its action in the central nervous system. (JTX30 at 507-08; Tr. 415:5-416:19.)

330. Unlike Weinstock 1981, Elmalem drew a quantitative comparison of the relative effects of different drugs in a head-to-head study. (Tr. 256:3-10, 415:23-417:14; JTX21 at 1059.)

331. The purpose of a study is significant because it dictates what experimental protocol is appropriate. (Tr. 410:10-18.)

332. While a POSA would have understood that in view of its purpose, Elmalem made "[a]ll drugs" from a stock sterile saline solution, Weinstock 1981 discloses that "[m]orphine and physostigmine were made up freshly for each experiment." (JTX30 at 505; Tr. 568:13-571:19.)

D. Neither The '807 Patent Nor Elmalem Teaches Or Reasonably Suggests Rivastigmine Undergoes Oxidative Degradation Or Requires An Antioxidant In A Transdermal Device

333. Dr. Kydonieus admitted that the '807 Patent "does not discuss transdermal formulations" (Tr. 249:16-18); the '807 Patent only discloses compositions for administration orally and/or by injection. (Tr. 355:19-356:15; JTX17 at 7:15-19.)

334. The disclosure of antioxidants in the '807 Patent is limited to "[s]terile compositions for injection." (JTX17 at 7:45-53; Tr. 363:2-364:9.)

335. Elmalem does not disclose transdermal formulations; it only discloses aqueous formulations for injection. (Tr. 257:14-19, 372:22-374:18; JTX21 at 1060.)

336. Dr. Kydonieus conceded that in transdermal formulations, the drug is "not in water solution"—*i.e.*, the drug is not in aqueous solution. (Tr. 186:11-24; *see also* Tr. 358:15-21,

385:2-387:17.)

337. As of 1998, no commercial transdermal formulation included an aqueous solution. (Tr. 358:15-21.)

338. Dr. Kydonieus admitted that "you cannot extrapolate directly from one formulation to the other." (Tr. 258:1-7.)

339. Dr. Kydonieus admitted that "if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch" because oxidation "is formulation dependent." (Tr. 258:8-13.)

340. Dr. Schöneich admitted that "whether [rivastigmine] actually degrades and at which rate, that depends on how the formulation is made up." (Tr. 94:21-95:6.)

341. Dr. Kydonieus in his expert report stated: "the mere possibility of an effect is very different from showing an actual effect in a specific transdermal system" because oxidative degradation "depends on the formulation." (Tr. 228:6-21.)

342. Dr. Klibanov testified that the difference between parenteral and transdermal formulations "was highly relevant . . . because . . . one of the basic principles of pharmaceutical formulations is that the stability of a drug very much depends on the formulation in which it is present and on the conditions." (Tr. 357:5-358:14.)

343. All experts agreed that "the stability of a drug, including stability toward oxidative degradation, is formulation specific" and testing would have been required to determine whether rivastigmine degrades under pharmaceutically relevant conditions. (Tr. 453:19-454:9; *see also* Tr. 95:24-96:18, 232:6-13, 258:8-13, 283:12-284:17, 318:8-319:9, 358:4-14; SOF 253.)

344. A drug may be unstable in aqueous solution for injection, but stable in a transdermal formulation. (Tr. 358:4-14.)

345. Physostigmine requires an antioxidant in aqueous solution but does not require one in a transdermal formulation. (Tr. 366:19-368:24, 466:8-468:7; PTX190 at 4:32-60; JTX33 at 8:50-65.)

346. Even if the '807 Patent and/or Elmalem suggested that rivastigmine required an antioxidant in aqueous solution, that would not have reasonably suggested to a POSA that rivastigmine also required an antioxidant in a transdermal formulation. (Tr. 366:6-18, 418:9-419:19.)

IV. A POSA Would Not Have Reasonably Expected Rivastigmine To Oxidative Degrade Based On Its Structure

347. A POSA as of 1998 would have known that essentially all organic compounds can undergo oxidative degradation under sufficiently harsh conditions (*e.g.*, burning). (Tr. 319:23-321:4.)

348. The structure of RA_7 had been known since 1986 (the publication date of EP '926). (Tr. 369:16-371:5; PTX194 at [43]; JTX19 at 2.)

349. The structure of rivastigmine had been known since 1988 (the publication date of GB '040). (JTX19 at [43]; Tr. 45:14-24, 139:22-140:7, 350:13-351:10.)

350. Dr. Kydonieus admitted that "none of the references . . . specifically state that the structure of rivastigmine suggest[s] susceptibility to oxidation." (Tr. 239:24-240:17.)

A. A POSA Would Not Have Reasonably Expected Rivastigmine To Oxidatively Degrade Based On A Theoretical "Susceptibility"

351. Dr. Schöneich admitted that "susceptible to oxidative degradation" means only that "there is the potential for oxidative degradation at the site." (Tr. 94:2-15.)

352. Dr. Schöneich admitted that "whether [oxidative degradation of rivastigmine] actually happens, that needs to be shown experimentally and the extent to what it happens needs to be shown experimentally." (Tr. 95:24-96:18.)

353. Dr. Kydonieus admitted that simply knowing "a compound . . . is susceptible to oxidation" "doesn't tell you how much degradation you will get period depending on that formulation." (Tr. 231:21-232:13.)

354. Chemical Stability of Pharmaceuticals states: "Kinetically . . . there is a sufficient energy barrier to many [oxidation] reactions (the energy of activation) that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation." (JTX22 at 82; Tr. 454:10-455:22.)

355. Dr. Klibanov testified that "even though theoretically a molecule may undergo oxidative degradation, [] as a matter of reality, due to this high kinetic barrier, it may not do so at a measurable rate." (Tr. 454:10-455:22; *see also* Tr. 319:23-321:4.)

B. A POSA Would Have Known That Oxidation Is Complex, Poorly Understood, And Unpredictable

356. A POSA would have known that oxidation reactions were not well understood. (Tr. 420:18-421:15; JTX22 at 82 (Chemical Stability of Pharmaceuticals: "Our overall mechanistic understanding of oxidative and photochemical reactions is poor.").)

357. Modern Pharmaceutics, published in 1996, teaches: "The mechanisms of oxidation reactions are usually complex, involving multiple pathways for the initiation, propagation, branching, and termination steps." (PTX153 at 183; Tr. 420:18-421:15.)

358. Dr. Schöneich admitted that "very few detailed studies in regard to oxidative mechanisms of specific pharmaceuticals [had] been performed as of 1998." (Tr. 107:13-20.)

359. Dr. Schöneich admitted that he "[has not] seen any data that would allow [him] to answer the question of whether rivastigmine is susceptible to oxidative degradation in a transdermal formulation." (Tr. 95:7-13.)

360. At most, the prior art recognizes that an analysis of the chemical structure would identify

only "potential mode(s) of degradation." (PTX153 at 181; Tr. 421:20-422:20, 423:11-22.)

361. Modern Pharmaceutics lists functional groups that potentially may undergo oxidation, but none of the functional groups identified is present in rivastigmine, and the functional groups identified do not include the benzylic C-H bond or amines on which Drs. Schöneich and Kydonieus rely. (PTX153 at 183; Tr. 421:20-423:10.)

362. Drs. Schöneich and Kydonieus admitted that there is no stability data concerning rivastigmine available in the prior art literature. (Tr. 95:7-23, 233:5-11.)

363. All experts agreed that experimentation would have been required to determine whether a drug undergoes degradation in a pharmaceutical formulation because degradation is formulation specific. (SOF 253, 343)

364. Hydrolysis reactions are much simpler than oxidation reactions. (Tr. 391:15-392:3.)

365. Experiments to understand the mechanism of hydrolysis of carbamates had been conducted for decades (since the 1930s) and as of 1998, hydrolysis reactions of carbamates were much better understood than oxidation reactions. (Tr. 389:8-392:3; JTX26 at 133-34.)

C. A POSA Would Have Known That The Structure Of The Molecule As A Whole Determines Its Stability

366. As of 1998, a POSA would have known that the structure of the molecule as a whole determines its stability. (Tr. 316:2-317:7, 423:11-424:5; SOF 379, 449.)

367. The prior art taught that the structure of physostigmine as a whole determines its stability because it was known to be "a particularly labile compound because its two tertiary amine groups facilitate hydrolysis of its phenolic [carbamate] group," which groups are located on opposite sides of the molecule. (JTX33 at 3:51-54; Tr. 424:6-426:2.)

368. Dr. Klibanov explained that physostigmine illustrates "that the structure of the molecule as a whole, not just the particular presence of a particular group, [] affects the stability of the

molecule." (Tr. 424:6-426:2.)

369. Dr. Klibanov explained that "the same basic notion [that the structure of the molecule as a whole determines its stability] applies to other modes of degradation of drugs, including oxidative degradation." (Tr. 426:3-9.)

370. As of 1998, there were multiple real-world examples of drugs having the three structural features found in rivastigmine—a tertiary C-H bond adjacent to a benzylic group and a tertiary amine, but differing structurally in other respects—that were not reported to undergo oxidative degradation or to contain an antioxidant in their commercial formulations, including: hydroxyzine, meclizine, mirtazapine, and benzquinamide. (Tr.437:10-439:3; PTX157 at 1878, 1992, 2007, 2015, 2042.)

371. Mirtazapine was commercially available as a free base. (PTX157 at 1878.)

372. Hydroxyzine was commercially available in liquid (*e.g.*, a syrup, oral suspension, or solution for injection) formulations. (PTX157 at 1992, 2015, 2042.)

373. Ampicillin contains a tertiary C-H bond adjacent to a benzylic group and a primary amine but was not reported to undergo oxidative degradation or to contain an antioxidant in its commercial formulations. (Tr. 437:10-439:3; PTX157 at 2035, 2872.)

374. Ampicillin was commercially available as a free acid, *i.e.*, not a salt. (PTX157 at 2872.)

375. As of 1998, there were additional examples of drugs having a C-H bond adjacent to a benzylic group that were not reported to undergo oxidative degradation or to contain an antioxidant in their commercial or patented transdermal formulations, including: dexsecoverine, scopolamine, fentanyl, benztropine, and secoverine. (Tr. 439:21-440:22; PTX157 at 890, 1336; PTX185 at 5:55-7:10; PTX186 at 6:15-8:32.)

376. Absent reported instability, a POSA would believe that a commercially available drug

was stable. (Tr. 448:7-14.)

377. Since 1998, additional drugs having a C-H bond adjacent to a benzylic group have been approved by the FDA in formulations without a reported antioxidant, including: selegiline and buprenorphine. (Tr. 441:19-443:8; PTX188 at 903; PTX189 at 2684.)

378. Selegiline has a tertiary amine as well as a C-H bond adjacent to a benzylic group. (Tr. 294:9-11, 469:12-21.)

379. A POSA would have concluded from the examples in SOF 370-377 above that the presence of certain functional groups, such as a tertiary C-H bond with an adjacent aromatic group and tertiary amine, does not reasonably predict whether a drug will undergo oxidative degradation under pharmaceutically relevant conditions or require an antioxidant. (Tr. 441:5-18.)

380. The absence of any reported instability or an antioxidant in the examples provided in SOF 370-377 above would not be attributed to compounds being a salt because salts are sometimes more stable than bases and sometimes not; stability depends on the structure of the molecule as a whole, including the nature of the salt. (Tr. 461:21-462:11.)

381. The absence of an antioxidant in the examples provided in SOF 370-377 above would not be attributed to their dosage forms because oxidative degradation can occur in all dosage forms, including in solids and dry dosage forms. (Tr. 439:13-20.)

382. Remington's states that "[t]here are a number of reasons for formulating drugs in" a dry or solid dosage form other than to improve stability, including for "improved taste, low water solubility, palatability and ease of administration," and the potentially improved stability is not specific to oxidative stability. (JTX5 at 1519 (addressing other instabilities including hydrolysis and ingredient-ingredient or ingredient-container incompatibilities).)

383. In his expert reports, Dr. Schöneich cited dextromethorphan as a compound having a benzylic C-H bond that supported his structural theory. (Tr. 103:3-11, 443:14-444:13.)

384. At trial, Dr. Schöneich did not rely on dextromethorphan. (Tr. 103:3-11.)

385. A paper by Boccardi, published in 1994, states that dextromethorphan hydrobromide "is a very stable drug substance." (JTX24 at 433; Tr. 443:14-444:24.)

386. In a free radical test (*i.e.*, a test exposing the drug to free radicals that cause oxidative degradation), dextromethorphan hydrobromide showed "low reactivity . . . reflect[ing] the good stability of the substance." (JTX24 at 433; Tr. 443:14-444:24.)

387. A paper by Magid, published in 1963, states that dextromethorphan hydrobromide has "[e]xcellent stability" in pharmaceutical formulations and was reported to be stable in both solid (crystal) and liquid (aqueous solution) formulations when exposed to air and "[s]table under all normal conditions of storage" in tablets and capsules. (PTX180 at 621-22; Tr. 445:7-446:12.)

388. As of 1998, 17 dextromethorphan commercial formulations were available with no reported antioxidant. (Tr. 446:17-447:16; PTX157 at 672, 974, 1413, 1560, 1569, 1572, 1612, 1623, 1825, 1832, 1948, 2233, 2786, 2885.)

389. Based on the reported stability of dextromethorphan in the prior art, a POSA would have concluded that the presence of a benzylic C-H bond does not mean a compound will undergo oxidative degradation under pharmaceutically relevant conditions. (Tr. 447:18-448:14.)

D. A POSA Would Not Have Reasonably Expected Rivastigmine To Oxidatively Degrade Based On Nicotine

390. Dr. Schöneich admitted that he did not give "an opinion as to how many compounds existed as of 1998 that contained a benzylic carbon hydrogen bond" and did "not give[] an opinion as to how many compounds with a benzylic carbon hydrogen bond [had] been formulated in a pharmaceutical composition as of 1998." (Tr. 101:20-102:6.)

391. Dr. Schöneich admitted that while he also relied on dextromethorphan in his reports, at trial he "only focused on the compound nicotine" as an example of a compound "having a benzylic carbon hydrogen bond that [is] susceptible to oxidative degradation." (Tr. 103:3-13.)

392. Dr. Schöneich admitted that nicotine is "not a benzylic compound." (Tr. 104:3-10.)

393. Dr. Schöneich admitted that the chemical features around the tertiary carbon in nicotine are "distinct" from those in rivastigmine. (Tr. 104:11-105:7.)

394. Dr. Schöneich admitted that "technically speaking," nicotine does not have a benzylic C-H bond. (Tr. 103:14-104:10.)

395. Dr. Klibanov identified the following structural differences between rivastigmine and nicotine: rivastigmine contains a carbamate moiety and a benzene ring, nicotine does not; nicotine contains a tertiary amine in a ring structure, a pyrrolidine ring and a pyridine ring, rivastigmine does not; and rivastigmine contains a benzylic C-H bond, nicotine does not. (Tr. 448:15-451:24.)

396. A POSA would have reasonably expected rivastigmine and nicotine to have different stabilities because their structures are different and stability is influenced by the molecule as a whole. (Tr. 451:9-452:24.)

397. Real-world examples of other drugs having the three structural features found in rivastigmine—a tertiary C-H bond adjacent to a benzylic group and a tertiary amine, but differing structurally in other respects—existed in the prior art and were not reported to undergo oxidative degradation or to contain an antioxidant in their commercial formulations. (Tr.437:10-439:3; PTX157 at 1878, 1992, 2007, 2015, 2035, 2042, 2872.)

398. Nicotine was known to undergo oxidative degradation under some pharmaceutically relevant conditions. (Tr. 452:1-5.)

399. The Linnell paper, however, states that further work was needed to "provide more details on the mechanism of [nicotine's oxidation] reaction." (JTX32 at 91.)

400. Dr. Schöneich admitted that Linnell "did not study the stability of nicotine in a pharmaceutical composition." (Tr. 107:21-108:4.)

401. As of 1998, none of the three commercially available nicotine transdermal formulations was reported to contain an antioxidant. (Tr. 452:15-453:17; PTX157 at 884, 1439, 1568.)

E. The Inventors Of The '031 Patent Did Not Expect Rivastigmine To Oxidatively Degrade Based On Its Structure

402. Each of the '031 Patent inventors had a Ph.D. in their respective areas of expertise and quite some development experience. (Tr. 428:13-429:17.)

403. The '031 Patent inventors knew rivastigmine's structure and had much more experience with rivastigmine than a POSA would have had but did not expect that rivastigmine would undergo oxidative degradation. (Tr. 426:21-427:22, 428:13-429:23, 431:18-433:18; PTX246 at 70.)

404. The '031 Patent inventors assigned a very low probability encountering any chemical or physical instability or other problem with the quality of the rivastigmine base. (Tr. 431:18-433:20; PTX246 at 70.)

405. The '031 Patent inventors prepared several different rivastigmine transdermal formulations without an antioxidant. (Tr. 429:18-431:2; PTX242 at 244.)

406. The '031 Patent inventors' initial transdermal formulations without an antioxidant contained both rivastigmine base and rivastigmine salt. (Tr. 428:13-429:17; PTX242 at 244.)

407. The absence of an antioxidant in the '031 Patent inventors' initial rivastigmine formulations is consistent with a POSA's understanding that an antioxidant would not be required because the problem of oxidative degradation was not known or reasonably suggested

in the prior art and that an antioxidant would not be added unless required. (Tr. 431:8-17.)

408. Through testing, the '031 Patent inventors unexpectedly discovered two unknown degradation products of rivastigmine (ENA713). (PTX242 at 244; Tr. 433:22-435:4.)

409. The '031 Patent inventors conducted further testing to characterize the degradants and discovered "after exhaustive testing that [rivastigmine] is susceptible to degradation, particularly in the presence of oxygen." (JTX1 at 1:22-24; PTX242 at 244-45; Tr. 433:22-435:4.)

410. Through testing, the '031 Patent inventors discovered that an antioxidant could reduce rivastigmine's oxidative degradation. (JTX1 at 4:11-30; PTX242 at 245; Tr. 435:6-10.)

411. "Before the finding by the ['031 Patent inventors] that an antioxidant is necessary in compositions of [rivastigmine], it was hitherto thought unnecessary." (JTX1 at 4:8-10.)

V. A POSA Would Not Have Added An Antioxidant To A Rivastigmine Transdermal Patch Unless One Was Required

412. There are many types of degradation, including degradation by acids, by strong bases, by water (hydrolysis), by light (photochemical degradation), by heat (pyrolysis), and by oxygen (oxidation). (Tr. 314:24-315:16, 330:8-23; PTX153 at 181-85.)

413. Not all drugs undergo all types of degradation, and most drugs do not undergo any type of degradation under pharmaceutically relevant conditions. (Tr. 314:24-315:16, 330:8-23.)

414. Most drugs do not undergo oxidative degradation under pharmaceutically relevant conditions. (Tr. 314:24-315:16, 329:15-330:2.)

415. Pharmaceutically relevant conditions are the conditions encountered during drug manufacture, storage or administration. (Tr. 330:3-7.)

416. In the absence of any teaching or reasonable suggestion that there was a need to stabilize a drug, a POSA would not have attempted to solve an unknown stability problem. (Tr. 314:24-315:16.)

417. There is no prior art evidence or test data demonstrating or reasonably suggesting that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions. (Tr. 314:17-23, 315:17-316:1, 331:11-24; *see also* Tr. 95:7-23, 233:5-11.)

418. To determine whether rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions, a POSA would have had to conduct testing and the outcome of that testing would not have been reasonably predicted in advance. (SOF 253; Tr. 318:8-319:9, 330:24-331:10; *see also* SOF 363.)

419. Whether a drug undergoes oxidative degradation and the rate of oxidation can only be established experimentally, and a POSA would not have reasonably predicted the outcome of that experimentation in advance. (SOF 253; Tr. 96:10-97:2, 318:8-319:9, 454:10-456:8.)

420. As of January 1998, there were many different excipients in many different categories. (Tr. 361:2-362:17; JTX17 at 7:15-53; DTX91 at 84-87 (listing 33 categories of excipients).)

421. A POSA would not have added an excipient, including an antioxidant, to a composition unless one was needed. (Tr. 341:1-11, 361:2-362:17.)

422. Dr. Kydonieus admitted that "you don't want to put any chemicals including antioxidants into [formulations] that you don't need." (Tr. 237:21-238:6.)

423. Excipients are inactive ingredients that "contribute to the physical form, texture, stability, taste and overall appearance" but have no therapeutic benefit themselves and may be problematic. (DTX91 at 83; Tr. 344:16-346:7, 361:2-362:4.)

424. The EMEA guidelines, published in 1997, state with respect to including an antioxidant in pharmaceutical formulations: "Antioxidants should only be included in a formulation if it has been proved that their use cannot be avoided"; and "Antioxidants should not be used to disguise poorly formulated products or inadequate packaging." (PTX162 at 1-2; Tr. 341:12-342:22.)

425. The EMEA guidance is applicable to all dosage forms, including transdermal formulations. (Tr. 342:14-18.)

426. The EMEA guidelines further state: "The properties of [antioxidants] are due to certain chemical groups which are usually aggressive towards living cells and which lead to certain risks when used in man (and animals)." (PTX162 at 1.)

427. The '376 Patent, issued in 1987, likewise states: "[Adding an antioxidant] is not an acceptable approach with many known antioxidant agents which tend to be somewhat toxic (even if only mildly so) . . . ." (PTX184 at 2:60-68; Tr. 343:3-344:11.)

428. The '376 Patent further states: "Even aside from the problem of toxicity, it is generally undesirable to treat with a drug composition containing any bio-active component which is not absolutely essential to achieve the desired therapeutic effect." (PTX184 at 3:3-7; Tr. 343:3-344:11.)

429. A POSA would have understood from the prior art that "you wouldn't add an antioxidant unless you had to." (Tr. 341:12-342:22, 343:3-344:11; SOF 422.)

430. As of 1998, there were ways to reduce oxidative degradation without an antioxidant, including using nitrogen or carbon dioxide to exclude oxygen, an occlusive polymer matrix or an occlusive backing layer in a transdermal device, and/or an oxygen scavenger within the sealed pouch containing the transdermal device. (Tr. 348:1-349:20; JTX5 at 1507; JTX14 at 6:25-34, 8:4-8; JTX16 at 2:37-51.)

431. A POSA would have understood that these alternatives to using an antioxidant were preferable because they do not require the addition of an excipient to the drug formulation. (Tr. 348:1-349:4.)

432. A POSA would have had to conduct experiments to determine which, if any, of these

alternatives to an antioxidant would reduce oxidative degradation. (Tr. 349:5-13.)

433. Antioxidants may also increase, rather than decrease, drug degradation. (Tr. 344:16-19.)

434. An excipient may be incompatible with the drug or other excipients. (Tr. 344:16-346:7; JTX5 at 1507 (Remington's: "Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation.").)

435. If an excipient is incompatible with a drug, it may reduce the potency of the drug or degrade the drug. (Tr. 345:21-346:3.)

436. Chemical Stability of Pharmaceuticals provides a specific example of antioxidant incompatibility: "sulfites [a type of antioxidant] can readily form inactive addition compounds as with, for example, epinephrine." (PTX156 at 97; Tr. 346:12-347:10.)

437. Chemical Stability of Pharmaceuticals further states: "Thus not all antioxidants can be used with all drugs." (PTX156 at 97; Tr. 346:12-347:10.)

438. A POSA would have understood that antioxidants may unpredictably increase drug degradation rather than protect the drug from degradation. (Tr. 346:12-347:6.)

439. A POSA would not have reasonably predicted incompatibility without testing. (Tr. 347:15-24; PTX156 at 97 ("The correct choice [of antioxidant] is usually based on extensive stability testing . . . .").)

440. The Handbook simply lists excipients that have previously been used in pharmaceutical products; it is not specific to rivastigmine. (Tr. 180:13-181:2, 484:21-485:19.)

441. The Handbook would not have told a POSA that rivastigmine could be combined with an antioxidant. (Tr. 485:8-19.)

442. The '807 Patent would not have told a POSA that rivastigmine would be compatible with an antioxidant because it does not combine rivastigmine or RA_7 with an antioxidant. (Tr. 255:3-

6, 485:20-486:9.)

443. Elmalem would not have told a POSA that rivastigmine would be compatible with an antioxidant because it discloses no compatibility tests or stability data and the formulations were "made up freshly" indicating that they were used shortly thereafter. (Tr. 256:15-19, 486:10-487:3; JTX21 at 1060.)

444. GB '040 would not have told a POSA that rivastigmine is compatible with an antioxidant because it contains no compatibility information and does not disclose or reasonably suggest adding an antioxidant to rivastigmine. (Tr. 487:4-11, 489:17-490:16.)

445. Sasaki would not have told a POSA that rivastigmine would be compatible with an antioxidant because Sasaki does not disclose rivastigmine or RA_7 and "does not include any rivastigmine stability data." (Tr. 278:13-279:3, 463:17-18.)

VI. Sasaki Would Not Have Motivated A POSA To Combine Rivastigmine With An Antioxidant In A Transdermal Device

446. As of 1998, there were many thousands of known amine-containing drugs, many of which were not reported to undergo oxidative degradation. (Tr. 460:11-22, 465:12-466:4.)

447. As of 1998, a POSA would not have reasonably expected from its tertiary amine that rivastigmine would oxidatively degrade under pharmaceutically relevant conditions. (Tr. 461:11-20.)

448. There were multiple examples of pharmaceutical compounds in the prior art having a tertiary amine that were not reported to contain an antioxidant in their commercial or patented transdermal formulations, including: dexsecoverine, scopolamine, fentanyl, benztropine, secoverine, physostigmine. (Tr. 466:8-467:6, 467:17-468:7; PTX157 at 890, 1336; PTX185 at 5:55-7:10; PTX186 at 6:15-8:32; JTX33 at 8:50-65.)

449. From the prior art examples, a POSA would have concluded that stability towards

oxidative degradation depends on the structure of the molecule as a whole, not simply the presence of an amine, and that testing would be required to determine whether oxidative degradation would occur. (Tr. 460:11-22, 467:7-16.)

450. Since 1998, additional drugs having a tertiary amine have been approved by the FDA in commercial transdermal formulations without a reported antioxidant, including: oxybutynin, selegiline, and buprenorphine. (Tr. 468:8-470:1; PTX187 at 59; PTX188 at 903; PTX189 at 2684.)

451. Dr. Kydonieus admitted that if he "saw a tertiary amine on a compound, [he] would not . . . know whether or not that compound was susceptible to oxidative degradation." (Tr. 282:11-17.)

452. Sasaki would not have informed a POSA that rivastigmine would undergo oxidative degradation due to the presence of its amine group. (Tr. 462:12-463:10.)

453. Sasaki is not a peer reviewed publication; it is a Japanese "Unexamined Patent Application." (Tr. 463:11-16; DTX12.)

454. Sasaki does not mention rivastigmine or RA_7. (Tr. 278:13-23, 463:17-18.)

455. Dr. Kydonieus admitted that "Sasaki does not include any rivastigmine stability data." (Tr. 278:24-279:3.)

456. Sasaki describes testing on two amine-containing compounds, diphenhydramine and ethylamino benzoate, in one transdermal formulation. (Tr. 463:19-465:5.)

457. A POSA would not "extrapolate from just two amines to many thousands of known amines," or "from one transdermal formulation to all possible transdermal formulations," that all amines undergo oxidative degradation in an acrylic adhesive. (Tr. 465:12-466:6.)

458. GB '040 Example 2 teaches that rivastigmine can be combined with an acrylic adhesive

("Non swellable acrylate polymer") and does not teach or reasonably suggest that rivastigmine will degrade or require an antioxidant in that transdermal formulation. (Tr. 470:10-471:16; JTX19 at 19.)

459. Dr. Kydonieus admitted that "it's [his] opinion that when rivastigmine [is] in an acrylic adhesive, it will not necessarily undergo oxidative degradation." (Tr. 282:24-284:17.)

VII. Ebert Would Not Have Motivated A POSA To Combine Rivastigmine With An Antioxidant In A Transdermal Device

460. A POSA would not have been motivated to combine the teaching in Ebert with rivastigmine. (Tr. 479:24-480:15.)

461. Ebert does not mention rivastigmine or RA_7. (Tr. 286:10-12, 472:12-473:9.)

462. Dr. Kydonieus admitted that Ebert does not disclose any stability data for rivastigmine or "discuss or state using an antioxidant with rivastigmine." (Tr. 286:13-22, 472:12-473:9.)

463. Ebert discloses a method for making a transdermal device containing "volatile or heat-sensitive drugs, enhancers, or other components that cannot be subjected to drying or heating, such as would occur in an oven." (JTX28 at 5:16-21; Tr. 286:24-287:11, 473:10-474:5.)

464. Dr. Kydonieus admitted that he did not "cite any literature showing that rivastigmine is a heat sensitive or volatile drug." (Tr. 289:14-17, 474:12-16, 480:16-482:22.)

465. Ebert also addresses manufacturing problems specific to nicotine transdermal formulations, including that with "above about 50% nicotine by weight[,] the [transdermal adhesive] fails to solidify properly" and "many of the common materials from which components of TDD devices, such as backings, adhesives, membranes, matrices, and release liners, are dissolved or degraded by nicotine." (JTX28 at 3:17-25, 4:1-4; Tr. 474:21-476:2.)

466. There is no evidence that rivastigmine suffered from any of the problems associated with nicotine addressed by Ebert. (Tr. 474:21-475:19.)

467. To address the problems in SOF 463 and 465 above, Ebert discloses an unconventional manufacturing process where nicotine is extruded as an "active gel" onto a dried adhesive layer. (Tr. 287:12-16, 476:4-478:11; JTX28 at 1:13-20, 19:34-20:3.)

468. To prepare the "active gel," Ebert mixes nicotine with hydroxyl propyl cellulose for an extended period of time (*e.g.*, 26.5 hours) in air. (Tr. 476:4-478:11; JTX28 at 19:34-20:12.)

469. Due to nicotine's "tendency to oxidize readily in the presence of light and air," Ebert adds an antioxidant during the mixing period. (Tr. 476:4-479:6; JTX28 at 19:17-20:3.)

470. If there were no need to prepare an "active gel" according to Ebert's method or if it was not known that a drug in that "active gel" required an antioxidant, a POSA would not have been motivated to use an antioxidant in Ebert's method. (Tr. 479:8-481:19.)

471. Ebert does not teach or reasonably suggest that any drug, other than nicotine, would undergo oxidative degradation or require an antioxidant. (Tr. 479:13-23.)

472. Conventionally, transdermal formulations are made using a matrix method where the drug is mixed with adhesive and then subjected to drying, which are referred to as "matrix-type" or "drug-in-adhesive" patches. (Tr. 289:18-290:19, 477:14-22.)

473. Dr. Kydonieus admitted that "90 percent of the patches are of the matrix type." (Tr. 290:16-19; *see also* Tr. 477:14-22.)

474. Dr. Kydonieus admitted that "it's conventional to use elevated temperatures to drive out the solvent when making a matrix-type patch." (Tr. 290:7-11; *see also* Tr. 477:14-22.)

475. GB '040 teaches that a rivastigmine transdermal device "may be manufactured in conventional manner" using a "conventional apparatus," which would include drying in a heating oven. (JTX19 at 10, 16, 19; Tr. 290:7-19, 481:20-482:22.)

476. GB '040 expressly directs a POSA to look to EP '229 for guidance on how to

manufacture a rivastigmine transdermal device. (Tr. 483:3-483:22; JTX19 at 16; JTX29.)

477. EP '229 does not disclose the use of an antioxidant in a transdermal formulation. (Tr. 483:20-22; JTX29.)

478. Dr. Kydonieus admitted that "Ebert was not the only patent relating to nicotine in a transdermal device as of 1998." (Tr. 291:11-14.)

479. Dr. Kydonieus admitted that he "did not do a patent search on nicotine transdermals to see how many transdermal nicotine formulations were out there and whether they included an antioxidant." (Tr. 291:15-18, 292:6-10.)

480. Dr. Kydonieus admitted that "the one patent that [he] relied on, the Ebert patent, was provided to [him] by Noven's lawyers." (Tr. 292:11-14.)

481. Dr. Schöneich admitted that for the three commercially available nicotine transdermal devices "the POSA can only conclude that [in these] particular formulations an antioxidant was not necessary." (Tr. 109:6-12, 110:17-111:8.)

482. Because the prior art did not teach or reasonably suggest that rivastigmine suffers from the problems addressed in Ebert, and GB '040 states that rivastigmine can be manufactured in a conventional manner, a POSA would not have been motivated to combine GB '040 with Ebert. (Tr. 472:12-473:9, 483:23-484:10.)

VIII. The '031 Patent Is Not Invalid For Obviousness-Type Double Patenting

483. The sole inventor of the '176 Patent is Albert Enz. (JTX20 at [75].)

484. The inventors of the '031 Patent are Bodo Asmussen, Michael Horstmann, Kai Köpke, Henricus L.G.M. Tiemessen, Steven Minh Dinh, and Paul M. Gargiulo. (JTX1 at [75].)

485. None of the claims of the '176 Patent discloses an antioxidant. (Tr. 491:19-21.)

486. The prior art would not have motivated a POSA to add an antioxidant to the claims of the '176 Patent. (Tr. 491:22-492:5.)

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